FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF FAMOTIDINE GASTRORETENTIVE TABLETS BY MELT GRANULATION TECHNIQUE

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: RAJIVGANTHI .A

REG.No. 261410275

Under the Guidance of

Dr. R. Sambathkumar, M.Pharm., PhD,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF FAMOTIDINE GASTRORETENTIVE TABLETS BY MELT GRANULATION TECHNIQUE",** submitted by the student bearing **Reg. No: 261410275** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

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Place: Kumarapalayam
Date:

Dr. R. Sambathkumar, M. Pharm., PhD.,
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DECLARATON

I do hereby declared that the dissertation **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF FAMOTIDINE GASTRORETENTIVE TABLETS BY MELT GRANULATION TECHNIQUE"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Dr. R. Sambathkumar, M. Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Mr. RAJIVGANTHI .A**

Date: **Reg.no. 261410275**

Dedicated to Parents, Teachers & My Family

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Mr. RAJIVGANTHI .A

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SYMBOL INDEX

Rpm	: Revolutions per minute
°C	: Degree celsius
Fig	: Figure
E.g.	: Example
Mg	: Milligram
Min	: Minutes
Ml	: Milliliter
µg	: Microgram
µg/ml	: Microgram per milliliter
%	: Percentage
SDN	: Standard deviation
$\mathbf{R^2}$	: Regression

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ABSTRACT

The aim of present work is to prepare floating tablets of famiotidne Hydrochloride using HPMC K4M, HPMC K15M and HPMC K100M as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Famotidine an a histamine H2 receptor antagonist and used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). The short half life of famotidine, shorter resident in stomach and multiple administration dose make famotidine a very good candidate for formulation of floating drug delivery system. Floating tablets of famotidine were prepared by melt granulation method using HPMC K4M, HPMC K15M and HPMC K100M. The floating tablets was evaluated such as weight variation, hardness, friability, thickness, drug content, , *invitro* buoyancy, drug polymer compatibility (IR study), and *invitro* dissolution studies of tablets. The micromeritic properties was found to be good, *invitro* buoyancy and *invitro* dissolution studies confirmed their good release nature. Formulation F4 prepared with of HPMC K100M shows a good *invitro* buoyancy lag time & floating time and *invitro* dissolution studies shows a 96.78% release for a period of 12 hrs. The data obtained in this study thus suggest that a floating tablets of famotidine are promising for sustained drug delivery which can reduce dosing frequency.

1. INTRODUCTION

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery system(GRDDS).GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose[(1)]. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem[(2)].

These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract [(3)]. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines [(4)].

Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs.

The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches:

(a) Low density form of the DF that causes buoyancy in gastric fluid [5].

(b) High density DF that is retained in the bottom of the stomach [6].

(c) Bioadhesion to stomach mucosa [7].

(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or Pharmaceutical excipients[8, 9].

(e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter [10].

1.1. ANATOMY AND PHYSIOLOGY OF STOMACH

Anatomy:

The stomach is an organ for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, capable of displaying a large expansion to accomadate food without much increase in intragastric pressure. Whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The opening nearer to esophagus is called as cardiac end characterized by pyrolic sphincter. Under fasting conditions the stomach is collapsed bag with residual volume of 50 ml and contains a small amount of gastric fluid and air.

Physiology:

Stomach is an expanded section of digestive tube between theoesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the other parts of the digestive tube; with the exception the stomach have an extra, oblique layer of smooth muscle inside the circular layer which aids in performance of complex grinding motions.

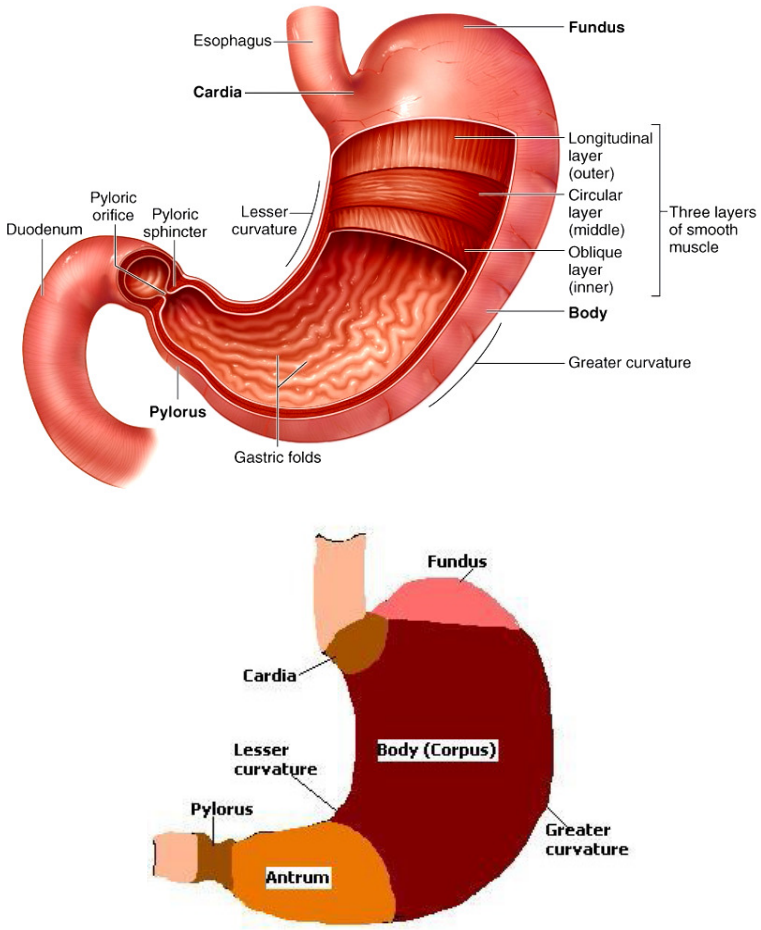


Fig.no.1. Internal structure of stomach

There are images to four types of secretary epithelial cells that cover the surface of the stomach and extended down into gastric pits and glands:

- Mucous cells: secrete alkaline mucous that protects epithelium against shear stress and acid.
- Parietal cells: secrete hydrochloric acid.
- Chief cells: secrete pepsin, a proteolytic enzyme.
- G cells secrete the hormone gastrin. The contraction of gastric smooth muscle serves two basic functions.

a. Ingested food is crushed, ground, mixed and liquefying to form chime.

b. Chime is forced through the pyloric canal in to the small intestine, a process called gastric emptying.

Mucosa:

When stomach is empty the mucous membrane lining is thrown in longitudinal folds or rugae, and when full the rugae are ignored out and the surface is a smooth velvety appearance there are numerous gastric glands situated below the surface in the mucous membrane consisting of the specialized cells that secrete gastric juice into the stomach.

Nerve supply:

The sympathetic supply to the stomach is mainly from coeliac plexus and parasympathetic supply is from vagus nerves. Sympathetic stimulation reduces motility of the stomach Under the physiological conditions, the gastric absorption of the drugs are insignificant as a result of the limited surface area covered by a thick layer of mucosal coating, the lack of villi on the mucosal surface, and the short residence time of the drugs in the stomach.

Blood supply:

Arterial blood is supplied to the stomach by branches of coeliac artery and venous drainage into the portal vein.

Gastric juice composition:

About 2 to 3 liters of gastric juice secreted daily by specialized cells in the mucosa. About 60ml with approximately 4 mmol of hydrogen ions per hour.

It consists of,

- Water
- Gastric enzymes(Pepsin, Gastric Lipase, Gastrin, Renin and other enzymes)
- Mucus- Glycoprotein
- Intrinsic factor
- Hydrochloric acid, Sodium, Calcium, Potassium, Chloride, Bicarbonate, Phosphate and Sulfate

Features of upper GIT:

Table no.1. Features of upper GIT

Section	Length(m)	Transit time(t)	P^H	Microbial count	Absorbing surface area(m^2)	Absorption pathway
Stomach	0.2	Variable	1-4	≤103	0.1	P,C,A
Small intestine	10^{-6}	3±1	5-7.5	103-1010	120-200	P,C,A,F,I,E,CM

Where,

P – Passive diffusion.

C – Aqueous Channel transport.

A – Active transport.

F – Facilitated transport.

I – Ion-pair transport.

E – Entero (or) pinocytosis.

Gastric pH:

Fasted healthy subject: 1.1 ± 0.15.

Fed healthy subject:3.6 ± 0.4.

Volume : Resting volume is about 25-50 ml.

Gastric emptying and motility:

Gastric emptying occurs during fasting as well as fed states. The passage of drug from stomach to the small intestine is called gastric emptying. It is the rate limiting step

for drug absorption because the major site for absorption in intestine. Generally rapid gastric emptying increase bioavailability of the drug. Faster onset requires for drugs that degrade in gastric environment. Delayed gastric emptying promotes dissolution of the drugs, which are poorly soluble drugs and for the drugs that is majorly absorbed from stomach or proximal part of the intestine. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases are,

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV Period of transition from phase III and phase I last for 0 to 5 minutes.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of myloelectric cycle (MMC) is delayed resulting in slowdown of gastric emptying rate [(11)].

Many Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Gastric Transit time:

The transit time of gastrointestinal drug delivery system along GI tract is the most limiting physiological factor in the development of controlled- release gastrointestinal drug delivery systems. The pattern of GI transit depends on the fasted or fed state.

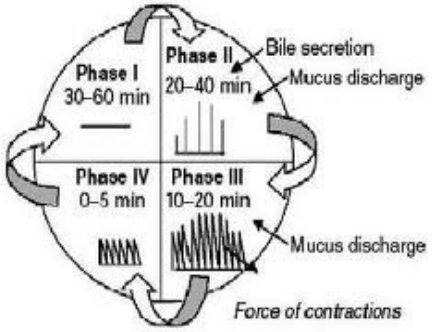


Fig no.2. Phase cycle

Requirements for gastric retention:

Physiological factors in the stomach it must be noted that to achieve gastric retention, the dosage form must satisfy certain requirements [(12)]. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must be resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

1.2. SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Drugs acting locally in the stomach,
  - E.g., Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach,
  - E.g., Amoxicillin
- Drugs that is poorly soluble at alkaline P^H,
  - E.g., Furosemide, Diazepam, Verapamil, etc.

- Drugs with a narrow window of absorption,
  - E.g., Cyclosporine, Methotrexate, Riboflavin and Levodopa, etc.
- Drugs which are absorbed rapidly from the GI tract,
  - E.g., Metronidazole, Tetracycline.
- Primarily absorbed from stomach and upper part of GItract,
  - E.g., Calcium supplements, Chlordiazepoxide and Cinnarazine
- Drugs that degrade in the colon[13],
  - E.g. Ranitidine, Metformin HCl, Metronidazole.
- Drugs that disturb normal colonic microbes,
  - E.g. Amoxicillin trihydrate - Antibiotics against Helicobacter pylori.

1.3. DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- **Drugs that have very limited acid solubility [13].**
  - E.g. Phenytoin etc.
- **Drugs that suffer instability in the gastric environment.**
  - E.g. Erythromycin etc.
- **Drugs intended for selective release in the colon.**
  - E.g. 5- amino salicylic acid and Corticosteroids etc.

1.4. Factors affecting the gastro retentive system [11]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system [11].

1. **Density**: Density of a dosage form plays a vital role in determining its buoyancy and henceforth, its floating efficiency.

2. **Shape of dosage form**: Compared to other shapes, devices with tetrahedron and ring shape have better floating potential. They have 90-98% better retention for 24 hrs.
3. **Single or multiple unit formulation**: Multiple unit formulations permit a larger margin of safety against dosage form failure compared with single unit dosage forms. Multiple unit formulations show a more predictable release profile and negligible impairing of performance due to failure of units.
4. **Fed or unfed state**: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.
5. **Nature of meal**: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release [(11)].
6. **Caloric content**: A meal rich in protein and fat content can increase floating by 4-10 hrs.
7. **Frequency of feed**: The floating can increase by over 400 minutes when successive meals are given compared with a single meal.
8. **Age**: Elderly people, above the age of 60, have a significantly longer floating.
9. **Posture**: Floating varies considerably between supine and upright ambulatory states of the patient.
10. **Concomitant drug administration**: Anticholinergics like Atropine, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride affect floating time.
11. **Biological factors**: Floating may vary as per health conditions or physiological status of a person.eg. Diabetes and Crohn's disease alters floating time.

1.5. Formulation considerations for GRDDS [(14)]

It must be effective retention in the stomach to suit for the clinical demand

1) It must have sufficient drug loading capacity.
2) It must be control the drug release profile.

3) It must have full degradation and evacuation of the system once the drug release is over[14].

4) It should not have effect on gastric motility including emptying pattern.

5) It should not have other local adverse effects.

1.5.1. Polymers and other ingredients [14]

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives.

Eg. Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M andK15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.

Inert fatty materials (5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy.

E.g. Beeswax, Fatty acids, Long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Effervescent agents*:* Sodium bicarbonate, Citricacid, Tartaric acid, Di-SGC (Di-Sodium GlycineCarbonate, CG (Citroglycine).

Release rate accelerants (5%-60%): eg.Lactose,Mannitol.

Release rate retardants (5%-60%): eg. Dicalciumphosphate, Talc, Magnesium stearate.

Buoyancy increasing agents (upto80%): eg. Ethylcellulose.

Low density material: Polypropylene foampowder (Accurel MP 1000®).

1.5.2. Advantages of gastroretentive delivery systems [17-19]

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. β-lactam antibiotics (Penicillins and Cephalosporins) [17].

- For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.
- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids [18].
- Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site specific drug delivery reduces undesirable Effects of side effects.
- Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index [19].
- Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
- Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
- The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

1.5.3. Disadvantages of floating drug delivery system [17]:

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water [17].
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

1.5.4. LIMITATIONS [18, 19]:

- Require a higher level of fluids in the stomach [18].
- Not suitable for Drugs that.
    - Have solubility problems in gastric fluid. E.g. Phenytoin,
    - Cause G.I irritation. E.g. NSAIDS,
    - Are unstable in acidic environment.
- Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and Corticosteroids etc.
- The floating systems in patients with achlorhydria can be questionable in case of swell able system [18].
- Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
- The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
- The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence [19].

1.5.5. Application of gastro retentive drug delivery systems [20]

- **Enhanced bioavailability**

  The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption. Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their

absorption [20].

Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

- **Enhanced first-pass biotransformation**

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

- **Sustained drug delivery/reduced frequency of dosing**

For drugs with relatively short biological half life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy [20].

E.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

- **Targeted therapy for local ailments in the upper GIT**

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

- **Reduced fluctuations of drug concentration**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate

release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index [20].

- **Improved selectivity in receptor activation**

  Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

- **Reduced counter-activity of the body**

  In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency [20].

- **Extended time over critical (effective) concentration**

  For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

- **Minimized adverse activity at the colon**

  Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for β-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

- **Site specific drug delivery**

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, Riboflavin and Furosemide.

E.g. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional Furosemide tablets.

1.6. Approaches to gastric retention [21]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems). Swelling and expanding systems, Mucoadhesive systems, High density systems, Modified shape systems, Gastric emptying delaying devices and co-administration of gastric delaying drugs. Among these, the floating dosage forms have been used most commonly [21].

Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents, Bioadhesive systems, enabling the localized retention of the system in the stomach, Swelling and expanding systems, preventing transit from the gastric sphincter, High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach, Super porous hydro gels, and Modified-shaped system. A number of other methods like use of passage-delaying agents, magnetically controlled systems and combination methods like floating-bioadhesive systems.

Floating drug delivery systems

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.

Types of floating drug delivery systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1) Non- Effervescent FDDS

2) Effervescent FDDS

1) Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion tomucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable Cellulose type hydrocolloids, Hydrophilic gums, Polysaccharides and Matrix forming materials such as Polycarbonate, Polyacrylate, Polymethacrylate, Polystyrene as well as Bioadhesive polymers such as Chitosan and Carbopol[21].

The various types of this system are as:

A. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

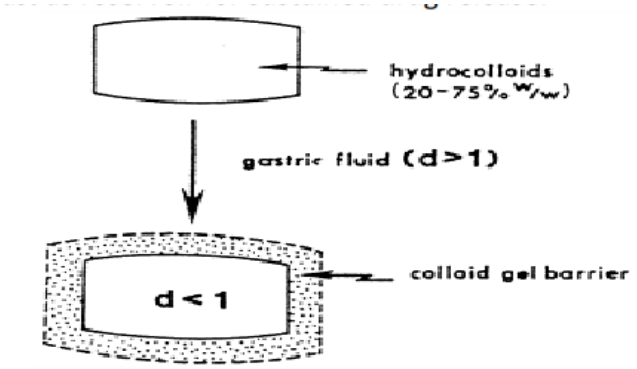


Fig. no.3. Single layer tablets

B. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose fromsystem while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gelbarrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[21].

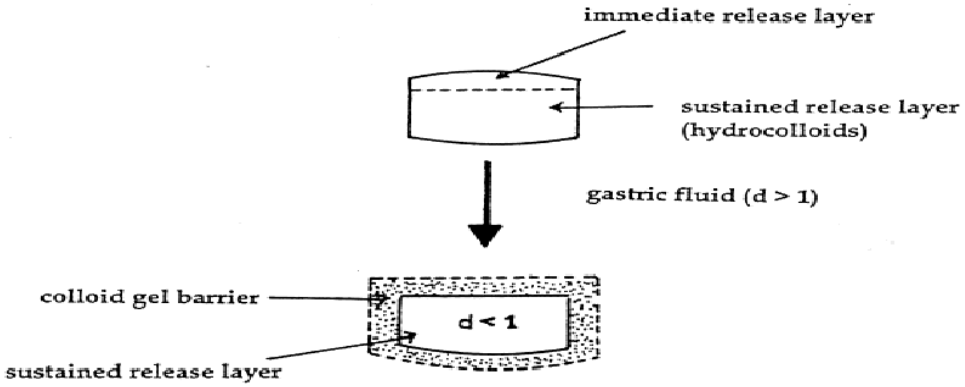


Fig.no.4. Bilayer floating tablets

C. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried Calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping Sodium alginate solution into aqueous solution of Calcium chloride, causing precipitation of Calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The Ethanol: Dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at400^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

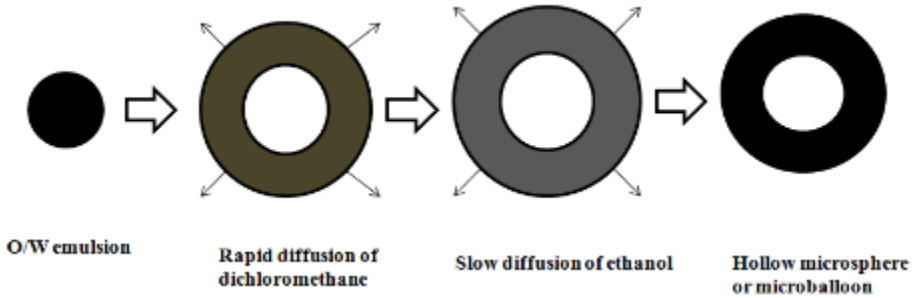


Fig.no.5. Hollow microsphere or microballoons

2) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. Citric acid and Tartaric acid) present in the formulation to produce Carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types:

1. Gas generating systems,
2. Volatile Liquid/Vacuum Containing Systems.

1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for Furosemide were developed by Ozdemir et al., 2000. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio.

One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The *in vitro* floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes[21]. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

B. Floating capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during *in vitro* tests as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

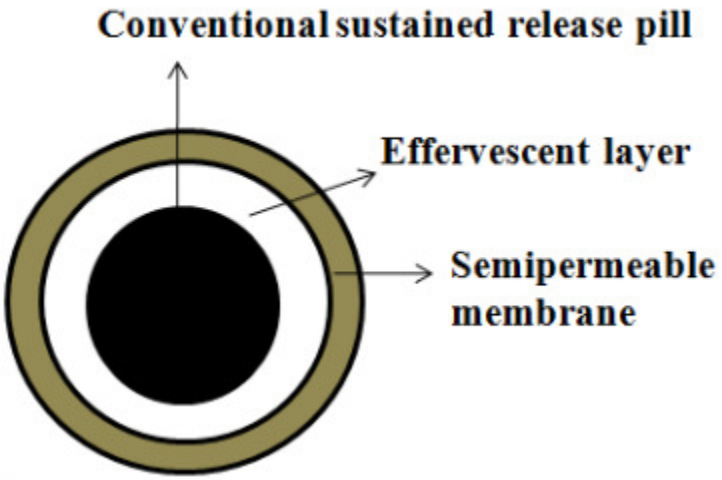


Fig.no.6. Effervescent (gas generating) system

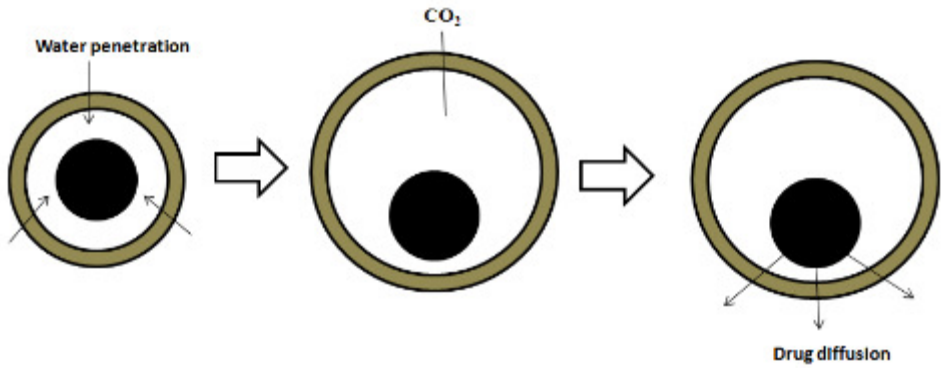


Fig.no.7. Drug release from gas generating system

C. Multiple unit type floating pills

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swell able membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

D. Floating system with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO_2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO_2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The *in vivo* behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

2. Volatile Liquid / Vacuum Containing Systems

A. Intra-gastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

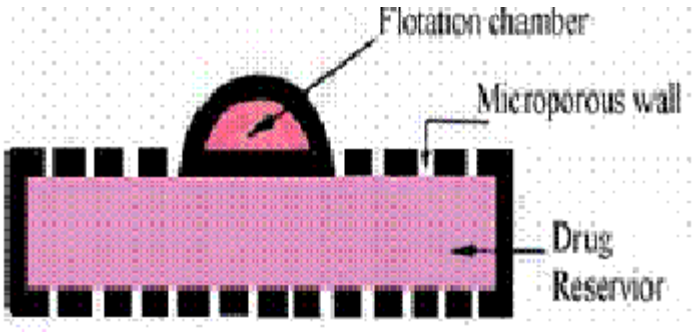


Fig.no.8. Intra-gastric drug delivery system

B. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule.

After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

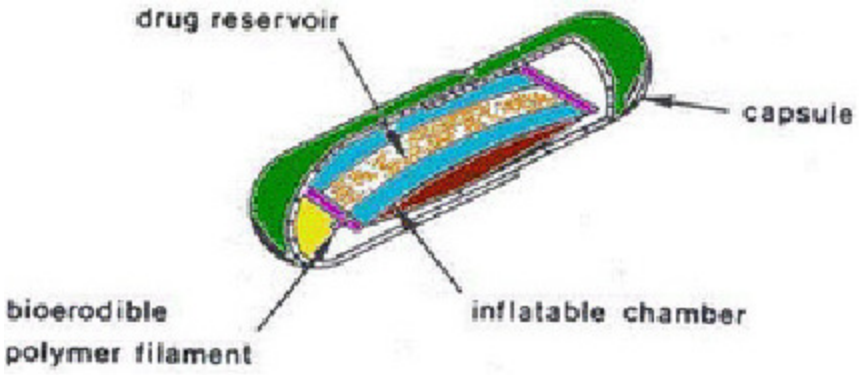


Fig.no.9. Inflatable drug delivery system

C. Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice.

The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt.

The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

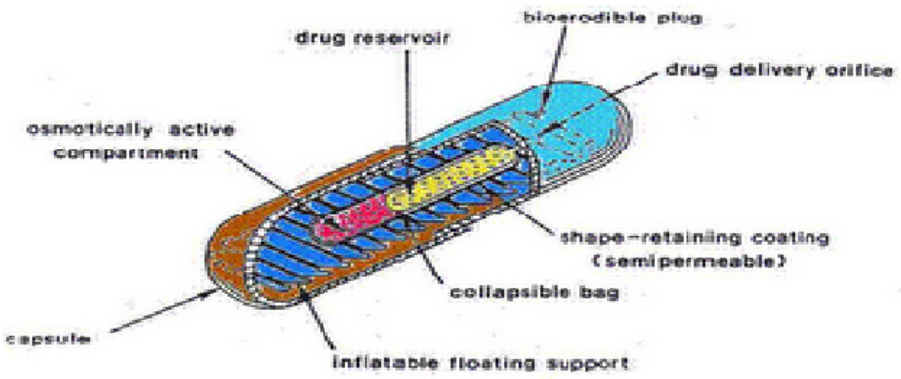


Fig.no.10. Intragastric osmotically CDDS

Bioadhesive drug delivery system

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a thorough understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment.

Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages [(21)]. The mucus layer, in addition to providing protection, provides a barrier to drug absorption. Various investigators have proposed different mucin-polymer interactions, such as Wetting and swelling of the polymer to permit intimate contact with the biological tissue. Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains. Formation of weak chemical bonds sufficient polymer mobility to allow spreading Water transport followed by mucosal dehydration.

As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time.

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.

Fig.no.11. Barrier formed by raft-forming system

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter.

Low-density systems (<1 g/cm^3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core.

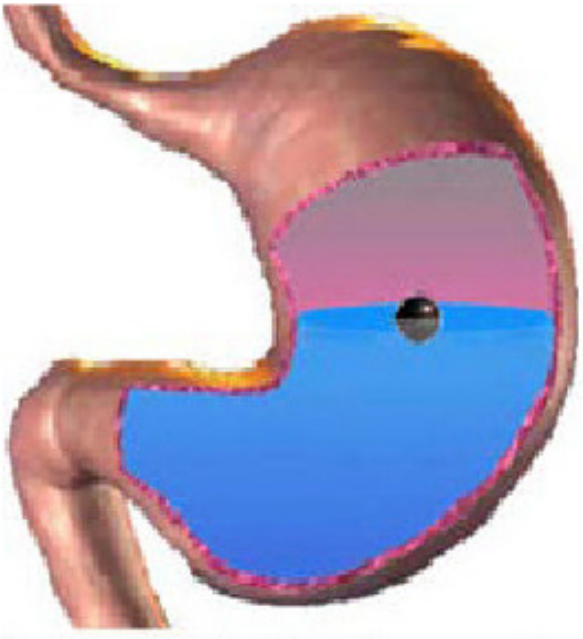


Fig.no.12. Low density system

Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers.

Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release.

Unfold able systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Caldwell et al., 1988 proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves.

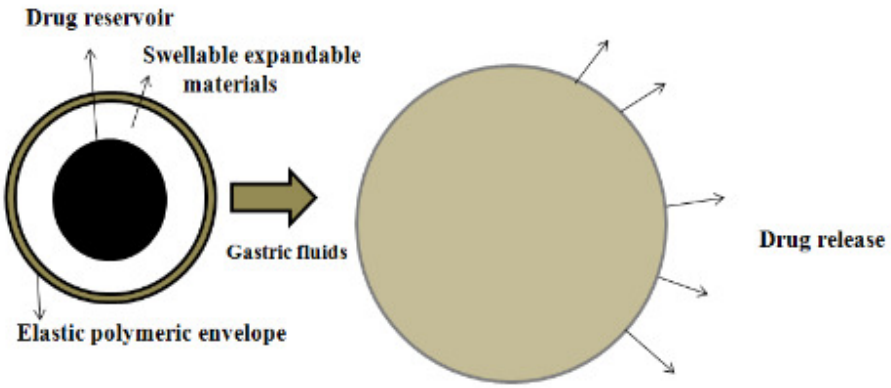


Fig.no.13. Drug release from swellable system

Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10 nm and 10 μm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur[21].

Superporous hydrogel, average pore size > 100 μm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di- Sol (crosscarmellose sodium).

Magnetic system

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach.

Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach.

A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect [21].

(1) The use of hydrogels swelling in contact with the gastric juice.

(2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane.

(3) Systems based on low-boiling liquids converting into a gas at the body temperature.

High density systems

Gastric contents have a density close to water (1.004 g /cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall[21].

A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time and Barium sulphate, Zinc oxide, Iron powder, Titanium dioxide are used as excipients.

1.7.FORMULATION INGREDIENTS OF FLOATING DOSAGE FORM[100]

Following types of the ingredients can be incorporated in to floating dosage form,

a) Hydrocolloids
b) Inert fatty materials
c) Release rate accelerants
d) Release rate retardant
e) Buoyancy increasing agents
f) Low density material
g) Miscellaneous

a. Hydrocolloids: Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

b. Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation andhence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and minaral oils can be used.

c. Release rate accelerants: The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

d. Release rate retardant: Insoluble substances such as dicalcium phosphate, talc, magnesium strearete decresesd the solubility and hence retard the release of medicaments.

e. Buoyancy increasing agents: Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

f. Low density material: Polypropylene foam powder

g. Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems

1.8.EVALUATION PARAMETERS OF FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo. However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

Floating time:

The test for floating time is usually performed in simulated gastric fluid or 0.1 mole.lit^{-1} HCl maintained at 37°C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

Drug release:

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Drug loading, drug entrapment efficiency, particle size analysis, surface characterization(for floating microspheres and beads):

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

Measurement of buoyancy capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media like deionised water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slower rate of hydration had
enhanced floating behaviour and which was more in simulated meal medium compared to deionised water.

Content uniformity, Hardness, Friability (Tablets):

These tests are performed as per described in specified monographs.

Resultant weight:

The in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by force equivalent to the force F required to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to quantify its floating or non floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the objects as shown in the equal

$F = F_{buoy} - F_{grav}$

$F = dfgV - dsgV = (df-ds)\ gv$

$F = (df - M/V)\ gV$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, df if the fluid density, ds is the object density is the object mass and V is the volume of the object.

X-Ray/Gamma Scintigraphy:

X-Ray/Gamma Scintigraphy is a very popularly used evaluation parameter for floating dosage form these days. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio- opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radio nucleide in a formulation allows indirect external observation using a γ-camera or scinti scanner.

Pharmacokinetic studies:

Pharmacokinetic studies are the integral part of the in vivo studies. Sawicki et al studied the pharmacokinetics of Verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional Verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-infinity) values (3.75 h and 364.65 $ng.ml^{-1}h$ respectively) for floating pellets were comparatively higher than those obtained for the conventional Verapamil tablets. (t_{max} value1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the C_{max} values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

Specific Gravity:

Specific Gravity of the floating system can be determined by the displacement benzene as a displacing medium

1.9. FUTURE POTENTIAL OF FDDS

Floating dosage form offers various future potential as evident from several recent publications. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parenteral

administration of drugs to oral pharmacotherapy would substantially improve treatment. It may be believed that it can be possible with FDDS. Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development of various anti-reflux formulations. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease, is also an important area of consideration. Combination therapy to treat *H.pylori* infection in a single FDDS needs to be developed. The study of the effect of various geometric shapes in a more excessive manner than previous studies on gastro retentivity needs to be developed. The investigations can be concentrated on the concept of design of novel polymers according to clinical and pharmaceutical need.

Table 2: Polymers used for development of floating drug delivery [101]

Tablets	Capsule	Microsphere/ Microparticles
Cellulosic hydrocolloids HPMC HPC HEC MC NaCMC	**Cellulosic hydrocolloids** HPMC HPC HEC NaCMC	**Cellulose derivative** Ethyl cellulose
Gel-forming hydrocolloids and matrix former Carbopol Carrageenan Gum guar Gum Arabic Sodium alginate Polyethylene oxide Polyvinyl lactam Polyarcylates, Polyvinyl acetate	**Gel-forming hydrocolloids and matrix former** Sodium alginate Carbopol Agar	**Gel-forming hydrocolloids and matrix former** Eudragit Polycarbonate, Polyacrylate, Polymethacrylate Polystyrene Chitosan Gelatin Alginate Gelucir

Polymers used in floating drug delivery[102]

1. Sustained Release Polymers are HPMC K100M, HPMC K15M, HPMC ELV, Polycarbonate, Polyethylene
2. glycol, Sodium alginate, Carbopol, Eudragit.
3. Effervescent Generating System: Citric acid, Tartaric Acid, Sodium Bicarbonate, Citroglycine.
4. Polymers which increase buoyancy: Ethyl cellulose
5. Polymers which decrease release: Talc, Magnesium Stearate, Dicalcium Phosphate.
6. Polymers which increase release: Mannitol, Lactose.
7. Inert Polymers: Long Chain Fatty Alcohol, Fatty Acid, Beeswax.
8. Polymers with low density: Foam powder of polypropylene.

Table 3: Commonly used drug in formulation of gastro retentive dosages forms

Commonly used drug in formulation of gastro retentive dosages forms [103]	
Dosage forms	**Drugs**
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p- Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil.
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several Acidic drugs
Films	Cinnerzine

2. LITERATURE REVIEW

- **Narasimharao *et al.,*** The oral route of administration of drugs is the most important method for achieving systemic effects. In the process of absorption of drug from oral route dissolution is the rate limiting step. Since the drug belongs to BCS class III, it is necessary to retard dissolution to ensure extended release of drug. Metformin hydrochloride is an anti diabetic, having an elimination half life of 5±2 hrs and its maximum daily dose is 1000mg. Hence it is an ideal candidate for extended release formulation. The objective of the study is to prepare metformin hydrochloride extended release tablets by direct compression technology using different polymer grades to achieve the desired dissolution pattern[21].

- **Kshirsagar *et al.,*** The objective of the present study was to develop a hydro dynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the in vitro buoyancy and in vitro release in simulated gastric fluid pH1.2. Effect of Carbopol as a release modifier was studied to ensure the delivery over a prolonged time period [23].

- **Eytan *et al.,*** Expandable gastroretentive dosage forms (GRDFs) have been designed for the past 3 decades. They were originally created for possible veterinary use, but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (GRT). After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating GRT of expandable GRDFs. Narrow absorption window drugs compounded in such

systems have improved in vivo absorption properties. These findings are an important step towards the implementation of expandable GRDFs in the clinical setting. [17].

- **Amit Kumar Nayak *et al.*** proposed that the purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfold able, super porous hydrogel and magnetic systems. Finally, advantages of gastroretentive drug delivery systems were covered in detail [3].

- **R Garg *et al.,*** proposed that Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion, sedimentation,

expansion or by a modified shaped system. The purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage forms [1].

- **Vinod *et al.*** proposed that much attention have been focused in pharmaceutical research in the area of gastroretensive oral drug delivery systems. Henceforth a wide spectrum of dosage forms have been developed for drugs which are unstable in alkaline pH, soluble in acidic pH, having a narrow absorption window, site of action specific to stomach. This article provides the entire classification of gastroretensive systems, formulation considerations for developing gastroretensive systems, factors affecting gastroretensive systems, merits and demerits, applications in pharmacy and a comparative diagrammatic representation limelight this article. Those gastroretensive systems which depend on liberation of carbondioxide show poor patient compliance because of flatulence and belching [2].

- **Nirav Rabadia *et al.,*** proposed that floating drug delivery systems (FDDS) was to show that how this drug delivery system is best for calcium channel blocker and to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the *invitro* techniques, *invivo* studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form [5].

- **Vaishali Sharma *et al.*** proposed that Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption in the GIT pioneered the idea of development of Gastroretentive drug delivery system. To design and evaluate the performance of GRDDS, it is important to understand the relevant anatomy and physiology of the GI tract. To

achieve gastric retention, the dosage form should satisfy certain requirements; primarily, the dosage form must be able to withstand the forceful peristaltic waves in the stomach and the constant contractions, grinding and churning. To function as a gastric retention device, it must resist premature gastric emptying. Once the purpose has been served, the device should be removed from the stomach with ease. Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (<~1.004 g/cm³), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Using FDDS one can easily increase the absorption of gastric secretion-labile drugs [6].

- **Shukla Shruti *et al.,*** proposed that the purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed [11].
- **Natasha Sharma *et al.*** proposed the concept behind the development of novel delivery system in certain drawback of conventional dosages form and to overcome the certain aspect related to physicochemical properties of drug molecule and related the formulation development. Controlled release floating drug delivery system is a promising delivery system for a drug candidate having limited absorption window sparingly soluble and insoluble drugs, drugs those locally release in stomach and shows degradability in colon or poor colonic

absorption. Floating drug delivery system comes under a gastroretentive drug delivery system that provides continuous controlled administration of sparingly soluble drugs at the absorption site. This review entitled the detailed scenario related to floating drug delivery system with their advantages over the conventional drug delivery system and also limitation, which are helpful in development of dosages form. Various types of techniques employed for development of this dosages form. Review focused on formulation aspect of effervescent floating drug delivery system with their evaluation techniques. The purpose of this comprehensive review is to compile the work going on this delivery system. Which provide the valuable information related to formulation aspect to achieve gastric retention and discussed the various factors affect and to overcome it [8].

- **Ravi P. Soni *et al.*** proposed that in recent years several advancement has been made in research and development of oral drug delivery system. The oral route achieved such popularity due to its ease of administration but has a drawback of non-site specificity. To overcome these limitations, gastric retentive drug delivery system is used. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention time. We have reviewed various gastro retentive approaches designed and developed until now i.e. floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, high density system, Raft forming system, magnetic systems. Among these systems, FDDS have been most commonly used. Finally, Evaluation, advantages, disadvantages, future potential and marketed preparation of gastro retentive drug delivery systems were covered[7].

- **Santosh Shep *et al.,*** proposed that Swelling Drug delivery system are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. In recent year's scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological

adversities like short gastric residence times and unpredictable gastric emptying times. Swelling drug delivery systems is the system which is retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Swelling dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Treatment of gastrointestinal disorders such as gastro-esophageal reflux. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate [18].

- **Shah S.H *et al.,*** proposed that the technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed [15].

3. AIM AND OBJECTIVE

The aim of the present study is to formulate and evaluate gastro retentive tablet of famotidine for the treatment of peptic ulcer, thus the action would be specifically in the stomach.

Famotidine is a histamine H2 receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Famotidine is available in different dosage forms, like tablets, solutions and injections. The dose of 20mg, 40 mg is available. Half-life of famotidine is around 2.5 to 3.5 hr, therefore it is used for floating sustained release of the drug is possible.

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery system. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.

These considerations have led to the development of a unique oral controlled release dosage form with gastroretentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and

prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.

Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines.

4. PLAN OF WORK

1. Literature survey.
2. Procurement of drug, polymer and other excipients.
3. **Preformulation studies:**
   - Organoleptic properties
   - Flow properties
   - Bulk and tapped densities
   - Measurement of powder compressibility
   - Melting point
   - P^H of the solution
   - Solubility
   - Drug-excipient compatibility
   - Preparation of standard curve
4. **Formulation of Famotidine tablets**
5. **Pre-compression parameters**
   - Angle of repose
   - Measurement of Bulk density and Tapped density
   - Measurement of Compressibility index and Hausner's ratio
6. **Evaluation of Famotidine tablets**
   - Evaluation of hardness
   - Thickness
   - Friability
   - Weight variation
   - Content uniformity
   - Buoyancy studies
   - *In-vitro* dissolution studies

5. DISEASE PROFILE - ULCER

INTRODUCTION:

Stomach ulcers, also known as gastric ulcers, are open sores that develop on the lining of the stomach.

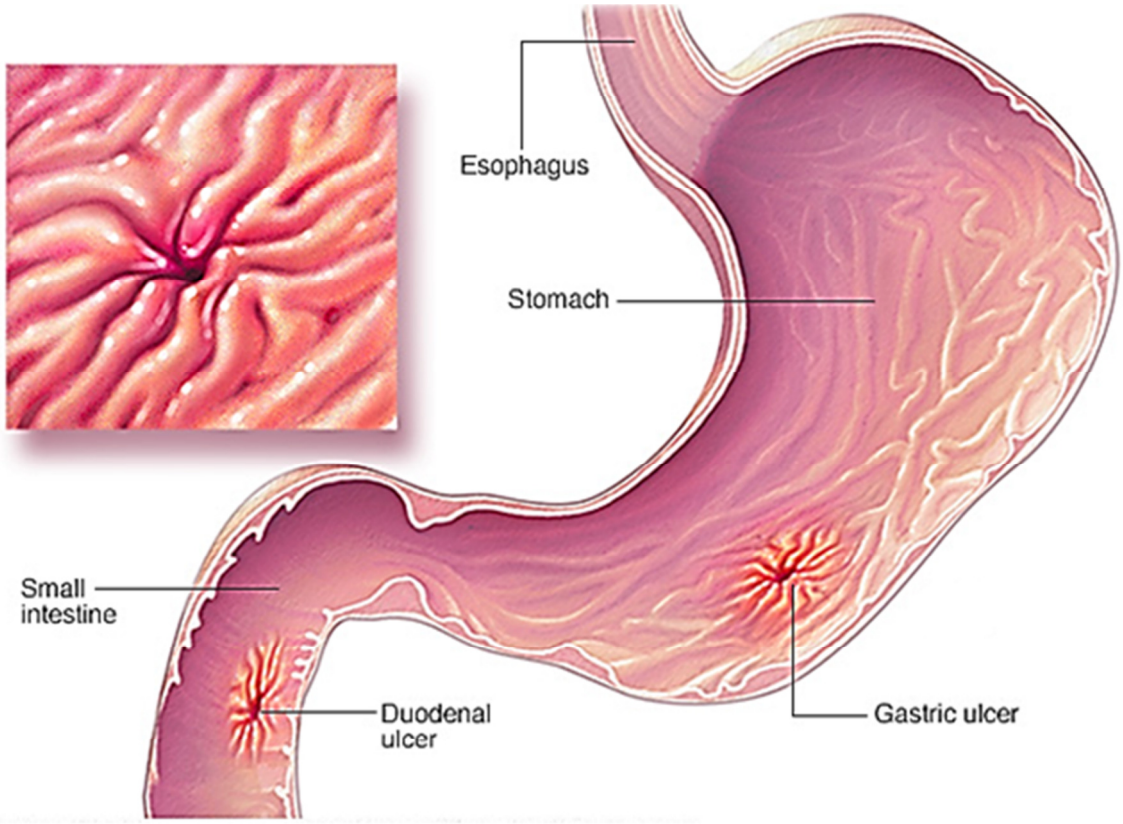
Ulcers can also occur in part of the intestine just beyond the stomach – these are known as duodenal ulcers.

Both stomach and duodenal ulcers are sometimes referred to as peptic ulcers. Here the term "stomach ulcer" will be used, although the information applies equally to duodenal ulcers.

Peptic ulcers include:

- **Gastric ulcers** that occur on the inside of the stomach
- **Duodenal ulcers** that occur on the inside of the upper portion of your small intestine (duodenum)

Fig.no.14. Peptic ulcer



SIGNS AND SYMPTOMS:

The most common symptom of a stomach ulcer is,

- Burning stomach pain
- Feeling of fullness, bloating or belching
- Fatty food intolerance
- Heartburn
- Nausea

The most common peptic ulcer symptom is burning stomach pain. Stomach acid makes the pain worse, as does having an empty stomach. The pain can often be relieved by eating certain foods that buffer stomach acid or by taking an acid-reducing medication, but then it may come back. The pain may be worse between meals and at night.

Nearly three-quarters of people with peptic ulcers don't have symptoms. Less often, ulcers may cause severe signs or symptoms such as:

- Vomiting or vomiting blood — which may appear red or black
- Dark blood in stools, or stools that are black or tarry
- Trouble breathing
- Feeling faint
- Nausea or vomiting
- Unexplained weight loss
- Appetite changes

However, stomach ulcers aren't always painful and some people may experience other symptoms, such as indigestion, heartburn and feeling sick.

CAUSES STOMACH ULCERS:

Stomach ulcers occur when the layer that protects the stomach lining from stomach acid breaks down, which allows the stomach lining to become damaged.

This is usually a result of :

a) H. pylori bacteria

H. pylori infections are common, and it's possible to be infected without realising it, because the infection doesn't usually cause symptoms. The bacteria live in the stomach

lining and people of all ages can be infected. However, in some people, the bacteria can irritate the stomach lining and make it more vulnerable to damage from the stomach acid.

b) NSAIDs

NSAIDs are medicines widely used to treat pain, a high temperature (fever) and inflammation (swelling).

Commonly used NSAIDs include:

- ibuprofen
- aspirin
- naproxen
- diclofenac

Many people take NSAIDs without having any side effects, but there's always a risk the medication could cause problems, such as stomach ulcers, particularly if taken for a long time or at high doses.

NSAIDs not to be used the person having a stomach ulcer. Paracetamol can often be used as an alternative painkiller, as it's generally considered safer.

c) Lifestyle factors

It used to be thought that stomach ulcers may be caused by certain lifestyle factors, such as spicy foods, stress and alcohol.

There is little hard evidence to confirm that this is the case, but these factors may make the symptoms of ulcers worse.

However, it is thought that smoking increases your risk of developing stomach ulcers and may make treatment less effective.

DIAGNOSIS:

The patient have an ulcer which will be identified, based on the symptoms. They will want to know if they are taking non-steroidal anti-inflammatory drugs (NSAIDs)and may test for an Helicobacter pylori (H. pylori) infection.

Next test is to perform a gastroscopy.

a) Testing for H. pylori infection

The symptoms may be caused by an H. pylori infection, they may recommend one of the following tests:

- urea breath test – you will be given a special drink containing a chemical that is broken down by H. pylori; your breath is then analysed to see whether or not you have an H. pylori infection
- stool antigen test – a small stool sample is tested for the bacteria
- blood test – a sample of your blood is tested for antibodies to the H. pylori bacteria (antibodies are proteins produced naturally in your blood and help to fight infection); this has now largely been replaced by the stool antigen test

If test positive for H. pylori, you will need treatment to clear the infection, which can heal the ulcer and prevent it from returning.

b) Gastroscopy

The procedure is carried out in hospital and involves passing a thin, flexible tube (an endoscope) with a camera at one end into your mouth and down into your stomach and first section of the small intestine (duodenum).

The images taken by the camera will usually confirm or rule out an ulcer. A small tissue sample may also be taken from your stomach or duodenum, so it can be tested for the H. pylori bacteria.

TREATEMENT:

- With treatment, most stomach ulcers will heal within a month or two. The treatment recommended for you will depend on what caused the ulcer.
- Most people will be prescribed a medication called a proton pump inhibitor (PPI) to reduce the amount of acid their stomach produces, and allow the ulcer to heal naturally.
- If an H. pylori infection is responsible for the ulcers, antibiotics will also be used to kill the bacteria, which should prevent the ulcer coming back.
- If the ulcers are caused by the use of NSAIDs, Alternative medication to NSAIDs, such as paracetamol, may be recommended.
- Stomach ulcers can come back after treatment, although this is less likely to happen if the underlying cause is addressed.
- An alternative type of medication, known as H2-receptor antagonists, is

occasionally used instead of PPIs, and sometimes you may be given additional medication called antacids to relieve your symptoms in the short term.

- They may have a repeat gastroscopy after 4 to 6 weeks to check that the ulcer has healed.
- With certain special lifestyle measures to take during treatment, but avoiding stress, alcohol, spicy foods and smoking may reduce the symptoms while ulcer heals.
- Some antacids also contain a medicine called an alginate, which produces a protective coating on the lining of the stomach.

Complications

Complications of stomach ulcers are relatively uncommon, but they can be very serious if they do occur. Some of the main complications are outlined below,

a)Internal bleeding

Internal bleeding is the most common complication of stomach ulcers. It can occur when an ulcer develops at the site of a blood vessel.

b) Perforation

A rarer complication of stomach ulcers is the lining of the stomach splitting open, known as perforation.

c) Gastric outlet obstruction

In some cases, an inflamed (swollen) or scarred stomach ulcer can obstruct the normal passage of food through your digestive system. This is known as gastric outlet obstruction.

Classification of anti-ulcer drugs

1. Reduction of gastric acid secretion:

a) H2 antihistaminics

Cimetidine, Ranitidine, **FAMOTIDINE**, Roxatidine, Loxatidine etc

b) Proton Pump Inhibitors

Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, esomeprazole etc

c) Anti-cholinergics

Pirenzepine, Propantheline, Oxyphenonium etc

d) Prostaglandin analogues

Misoprostil, Enprostil, Rioprostil etc

2. Neutralisation of gastric acid:

Antacids are used for neutralising the gastric acid in the stomach. These drugs are known as antacids.

a) Systemic antacids

sodium bicarbonate ($NaHCO_3$), sodium citrate etc

b) Non systemic antacids

Magnesium hydroxide ($Mg(OH)_2$), Magnesium trisilicate, Alminium hydroxide gel, Calcium carbonate ($CaCO_3$) etc

3. Ulcer protectives:

Ulcer protectives protect the ulcers by covering them and they consist of mainly polymers.

Sucralfate, Colloidal Bismuth subcitrate (CBS) etc

4. Ulcer Healing Drugs:

Carbenoxolone sodium

5. Anti H-Pylori drugs:

Ulcer is also caused due to the action of the bacterium Helicobacter Pylori, so for treating the ulcers caused by the bacterium, anti biotics are given.

Amoxicillin, Tinidazole, Tetracycline, Metronidazole, Clarithromycin

6. DRUG PROFILE

FAMOTIDINE

Famotidine, is a histamine H2 receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease.

Generic Name: Famotidine

Chemical Name: 3-[({2-[(diaminomethylidene)amino]-1,3-thiazol-4-yl}methyl) sulfanyl]-N'-sulfamoylpropanimidamide

Empirical Formula: $C_8H_{15}N_7O_2S_3$

Physical and Chemical Properties

Molecular weight - 337.449 g/mol,

Color – White to pale yellow crystals,

Nature -Crystalline powder,

Odour- Odourless,

Melting point- 163.5 °C,

Solubility- Freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

pKa - 12.4.

Pharmacokinetics: The bioavailability of oral doses is 40-45%. The apparent volume of distribution of the drug is reported to be 1.1-1.4 l/kg in adults and does not appear to be altered substantially in patients with renal dysfunction. Following oral or IV administration in rats, famotidine is widely distributed, appearing in highest concentrations in the kidney, liver, pancreas, and submandibular gland. The drug is 15-20% protein bound. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Clearance is renal cl=250-450 mL/min.

Indications and Dosage:

For the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD).

Dosage Oral:

40 mg orally once a day at bedtime OR 20 mg orally 2 times a day Maintenance dose: 20 mg orally once a day at bedtime. Duration of therapy: 4 weeks

Dosage Parenteral:

-Usual dose: 20 mg IV every 12 hours

Overdose:

Doses of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Contraindications:

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, PEPCID should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.

Mechanism of Action:

Famotidine binds competitively to H2-receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Drug Interactions: Some interacting drugs include atazanavir, dasatinib, delavirdine, certain azole antifungals (such as itraconazole, ketoconazole), pazopanib, among others.

Food Interactions: Avoid alcohol, Limit caffeine intake, Take without regard to meals, food may slightly increase the product's bioavailability.

Adverse Effects:

Adverse nervous system effects (eg, headache, dizziness) and GI effects (eg, constipation, diarrhea) occur most frequently during famotidine therapy. Although adverse effects of the drug generally are not severe, discontinuance of famotidine therapy

has been necessary in up to 14% of patients. Adverse effects generally are similar when famotidine is administered orally or IV.

Side Effects:

Some rare side may include, Headache, Upper respiratory tract infection, Vomiting, Nausea, Diarrhoea, Influenza like illness, Dizziness, Back pain, Constipation, Rash, Abdominal pain

7. EXCIPIENTS DATA

7.1 HYDROXYPROPYL METHYLCELLULOSE:

Nonpropritary names:

Hypromellose (BP), methylhydroxypropylcellulosum (EUR), hydroxypropyl methylcellulose (USP).

Synonym:

Cellulose,hydroxylpropyl methyl ester, culminalMHPC, E464,HPMC, Methocel, methocel, methylcellulose propylene glycol ether, methyl hydroxylpropylcellulose, metalose, pharmacoat.

Chemical Name and CAS Registry Number

Cellulose, 2-hydroxy propyl methyl ether, [9004-65-3]

Emprical Formula and molecular weight:

Hydroxypropyl methylcellulose is a partly as a O-methylated andnO-(2 hydroxylated) cellulose. Molecular weight varies from 10000 – 15000000.

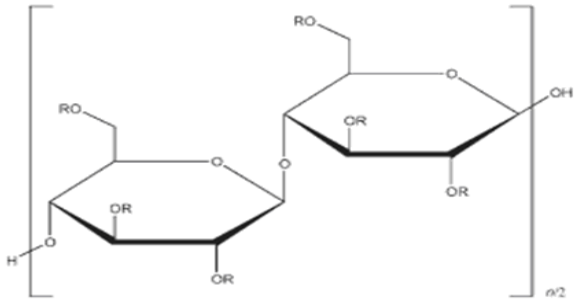
Description:

Hydroxypropyl methylcellulose is an odourless and tasteless, white or creamy-white coloured fibrous or granular powder.

Solubility:

Soluble in cold water, forming viscous colloidal solution. Practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane and mixtures of ethanol and dichloromethane

Structural formula:



Where R is H,CH_3 or[CH_3 CH(OH) CH_2]

Moisture content:

Hydroxypropyl methylcellulose absorbs moisture content from the atmosphere. The amount of moisture depends upon the initial moisture content, temperature and relative humidity on the surrounding air.

Viscosity content **:** 5-1000000 mPas (2%w/w solution at 20^{o}C).

The different commercial grades are available according to the viscosities,

Methocel K4M 4000 mPas

Methocel K15M 15000 mPas

Methocel K100M 100000 mPas

Density **:** Density (bulk) 0.341 g/cm3.
Density (tapped) 0.557 g/cm3.
Density (true) 1.326 g/cm3.

pH **:** 5.5-8.9.(1%w/w aqueous solution at 25^{o}).

Melting point **:** Browns at 190-200^{0C}, Chars at 225-230^{0}C.

Loss on drying **:** ≤5.0%

Burnt Residue **:** ≥1.0%

Specific gravity **:** 1.26.

Functional Category:

Coating agent, flim-former, stabilizing agent, suspending agent, tablet binder, vicosity increasing agent.

Applications in Pharmaaceutical formulation or technology:

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In Oral products, Hydroxypropyl methylcellulose is primarily used as a tablet binder, in flim-coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder.

Hydroxypropyl methylcellulose is used as a suspending and thickening agent in topical formulation (opthalmic preparation). It gives greater clarity compared to methyl cellulose so it is preferred in opthalamic formulation in conc. of 0.45-1.0% w/w used.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending

agent and stabilizing agent in topical gels and ointments.

In addition Hydroxypropyl methylcellulose is also used as an adhesive in plastic bandages.

Incompatabilities:

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts and organics to form insoluble precipitates.

Stability and storage conditions:

It is stable although it is slightly hygroscopic. The bulk material should be stored in air tight container in a cool and dry place.

Safety:

It is widely used in many oral and topical pharmaaceutical formualtions. It is generally regarded as an essentially Non-toxic and Non-irritant material although excessive consumption may have laxative effect.

7.2 WHITE BEES WAX

Nonproprietary names:

White Beeswax (BP), Beeswax, White (PhEur), White Wax (USP-NF).

Synonym:

Bleached wax; cera alba.

Chemical Name and CAS Registry Number

Bleached wax; cera alba; E901, [8012-89-3]

Emprical Formula and molecular weight:

Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C24 to C36 esterified with straight-chain acids. These straight-chain acids also have even numbers of carbon atoms up to C36 together with some C18 hydroxy acids. The chief ester is myricyl palmitate. Also present are free acids (about 14%) and carbohydrates (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids.

Description:

Tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odour is less intense.

Density **:** 0.95–0.96 g/cm3.

Melting point: 61–65^{0}C.

Solubility

Soluble in chloroform, ether, fixed oils, volatile oils, and warm carbon disulfide, sparingly soluble in ethanol (95%), practically insoluble in water.

Functional Category

Controlled-release agent, stabilizing agent, stiffening agent.

Incompatibilities

Incompatible with oxidizing agents.

Safety

White wax is used in both topical and oral formulations, and is generally regarded as an essentially nontoxic and nonirritant material. However, although rare, hypersensitivity reactions to beeswax have been reported.

Stability and Storage Conditions

When the wax is heated above 150^{0}C, esterification occurs with a consequent lowering of acid value and elevation of melting point. White wax is stable when stored in a well-closed container, protected from light.

7.3 SODIUM BICARBONATE

Nonpropritary names:

Sodium Bicarbonate (BP, USP), Sodium Hydrogen Carbonate (PhEUR).

Synonym:

Baking soda, E500, Effer-Soda, monosodium carbonate, sodium acid carbonate, sodium hydrogen carbonate.

Chemical Name and CAS Registry Number:

Carbonic acid monosodium salt**,** [144-55-8].

Emprical Formula and molecular weight:

Formula: $NaHCO_3$ MW: 84.01.

Description:

Sodium bicarbonate is an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms.

pH **:** 7.9-8.4. (5%w/w aqueous solution).

Solubility **:** Soluble in water in 1 in 11 ratio & insoluble in Ethanol and ether.

Moisture content **:** Sodium bicarbonate Moisture content less than 1%w/w.

Melting point **:** 270^0 C (With decomposition).

Functional Category : Alkalizing agent; therapeutic agent.

Applications in Pharmaaceutical formulation or technology:

Sodium bicarbonate is generally used in effervescent tablets and Granules is formulated with citric and/or tartaric acid. When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Sodium bicarbonate has also been used as a freeze-drying stabilizer and increase absorption of some drugs. It is used in oral rehydration salts and also in dialysis fluids.

Incompatabilities:

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide.

Stability and storage conditions:

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

Safety:

When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material. Excessive amounts of sodium bicarbonate disturb the body's electrolyte balance and orally ingested sodium bicarbonate neutralizes gastric acid may cause stomach cramps and flatulence.

7.4 MAGNESIUM STEARATE

Nonpropritary names:

Magnesium Stearate (BP, USP-NF, PhEUR).

Synonym:

Dibasic magnesium stearate, magnesium distearate, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid.

Chemical Name and CAS Registry Number :

Octadecanoic acid magnesium salt, [557-04-0]**.**

Emprical Formula and molecular weight:

Formula: $C_{36}H_{70}MgO_4$. MW: 591.24. Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, poorely flowing, cohesive powder, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility:

Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95%).

Melting point : 117–150^{0}C**.**

Functional Category: Tablet and capsule lubricant.

Applications in Pharmaaceutical formulation or technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Incompatabilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Stability and storage conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Safety:

Magnesium stearate is non-toxic for oral administration and larger consumption may result in laxative effect and mucosal irritation.

7.5 TALC

Nonpropritary names:

Purified Talc (BP), Talc (USP, PhEUR).

Synonym:

Altalc, hydrous magnesium calcium silicate, hydrous magnesium silicate, Imperial, magnesium hydrogen metasilicate, powdered talc, purified French chalk, Purtalc, talcum.

Emprical Formula and CAS Registry Number:

$Mg_6(Si_2O_5)_4(OH)_4$, [14807-96-6]

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Moisture content:

Talc absorbs insignificant amounts of water at 25^0C and at a relative humidity of 75%.

Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaaceutical formulation or technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, it is also widely used as a dissolution retardant. In topical preparations, talc is used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties. Concentrations used asDusting powder 90.0–99.0, Glidant and tablet lubricant 1.0–10.0, Tablet and capsule diluent 5.0–30.0.

Incompatabilities:

Incompatible with quaternary ammonium compounds.

Stability and storage conditions:

Talc is a stable material and may be sterilized by heating at 160^0C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Safety:

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. Talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products.

7.6 LACTOSE

Nonpropritary names:

Lactose (BP), Lactose Monohydrate (PhEUR, USP-NF).

Synonym:

CapsuLac, GranuLac, Lactochem, lactosum monohydricum, onohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 30GR, Tablettose.

Chemical Name and CAS Registry Number:

O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate, [10039-26-6]

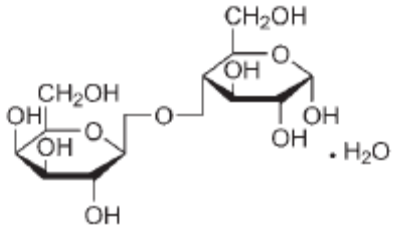
Emprical Formula and molecular weight:

Formula:$C_{12}H_{22}O_{11}\cdot H2O$. MW: 360.31

Description:

In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. αlactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting.

Structural formula:



pH **:**5.5-8.9.(1%w/w aqueous solution at 25^{o})

Solubility **:** Insoluble in chloroform, ethanol, ether. Soluble in water in ratio of 1 in 5.24.

Melting point: 201–202^{0}C (for dehydrated a-lactose monohydrate)

Moisture content:

Lactose monohydrate contains normally has a range of 4.5–5.5% w/w water content.

Functional Category:

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

Applications in Pharmaaceutical formulation or technology:

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.

Incompatabilities:

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

Stability and storage conditions:

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Safety:

Lactose is widely used as a filler and filler-binder in orals and injections. Adverse reactions to lactose are largely attributed to lactose intolerance, results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

8. MATERIALS AND EQUIPMENTS USED

8.1. MATERIALS USED:

Table no. 4. List of materials used

S.NO.	MATERIALS	SUPPLIER
1.	Famotidine	Molecules India Pvt.Ltd.
2.	HPMC K4M	Sooriyan pharmaceuticals., chennai
3.	HPMC K15M	Sooriyan pharmaceuticals., chennai
4.	HPMC K100M	Sooriyan pharmaceuticals., chennai
5.	Bees wax	Fine Chem, industries.
6.	Sodium bicarbonate	Fine Chem, industries.
7.	Lactose(monohydrate)	Standard chemicals
8.	Magnesium stearate	Advance labs
9.	Talc	Fine Chem, industries.

8.2. INSTRUMENTS USED:

Table no. 5. List of instruments used

S.No.	INSTRUMENTS	MANUFACTURER
1	Electronic balance	Shimadzu Corporation, AW220 &BX6205
2	FTIR spectrophotometer	Shimadzu Co UV-1700
3	UV/Visible spectrophotometer	Lab India UV 3000
4	Dissolution Apparatus(USP)	Electro lab Pvt. Ltd.
5	Tablet Hardness tester	Monsanto Hardness tester
6	Friability test apparatus	Roche Fribilator
7	Tap Density Apparatus	Erweka Pvt.Ltd
8	P^Hmeter	Systonic 335
9	Tablet compression machine	Proton Multipress
10	Vernier Caplier	Digimatic

9. PREFORMULATION

Preformulation studies are carried out in order to evaluate the physical and chemical properties of the drug alone and in the combined form with the excipients.

These studies are important to predict the physical and chemical properties and stability of the drug and excipients.

9.1. ORGANOLEPTIC PROPERTIES:

1. Colour:

Take a small quantity of sample and spread it on the white paper and examine it visually.

9.2. PHYSICAL PROPERTIES:

1. Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a file of the powder and the horizontal plan.

$$Ø = \text{Tan}^{-1} h/r$$

Where, h = height of file

R = radius of the base of the pile

Ø = angle of repose

Flow properties and corresponding Angle of Repose

Table No: 6. Flow properties and corresponding Angle of Repose

Flow property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	> 66

The ideal characteristics of a tablet that make it a popular and acceptable dosage form are compactness, physical stability, rapid production capability, chemical stability and efficacy. In general above characteristics of tablet are dictated by the quality of the granulation from which it is made. Many formulation and process variables involved in the granulation step can affect the characteristics of the granulation produced. Therefore various methods to measure certain granulation characteristics have been developed to monitor granulation suitability for tablet formulation. The main characteristics required to be monitored in granulation are flow properties and compressibility.

2. Determinations of bulk density and tapped density:

An accurately weighed quantity of the powder (w) was carefully poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus) the density apparatus was set for 500 taps and after that, the volume (v_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk Density} = W/V_0$$

$$\text{Tapped Density} = W/V_f$$

Where, V_0= Initial volume,

V_f = final volume

3. Compressibility index

The compressibility Index and Hausner ratio are measures of the property of a powder to be compressed. As such, they measure the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner ratio.

The compressibility index and hausner ratio are calculated by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:

$$\text{Compressibility index} = P_{tapped} - P_{bulk} / P_{tapped} X\ 100$$

$$\text{Hausner ratio} = P_{tapped} / P_{bulk}$$

Scale of flowability

Table No: 7. Scale of flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.10-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

4. Melting point:

It is the characteristic to test the purity of the sample.

Procedure:

Take a small quantity of sample into the fusion tube. Place the tube in the mating point apparatus containing castor oil. Increase the temperature of castor oil gradually and note the temperature starts to melt and when all the powder completely melts.

9.3. Solubility:

Take a small quantity of sample and add the solvent until the sample completely dissolves. It is examined visually for the presence of any un dissolved particles.

9.4.Drug-excipient compatibility studies:

Drug-excipient compatibility studies are important to know the interaction between drug and excipients and in between excipients of the formulation, which could later affect the stability of the formulation and may interfere with the pharmacological action of the drug.

The physical examination of the formulation is done when alone and in combination with the excipients. If there is any change in the physical appearance, shows that there is interaction.

But some substances do not show any physical changes when combined in a formulation, for such FT-IR (Fourier transform-infrared) studies are conducted.

Procedure by FT-IR studies:

The FT-IR studies are conducted for Famotidine and mixture of famotidine and excipients by preparing dispersion in potassium bromide discs. The peaks are obtained and compared with the standards by superimposing these spectra and observed for any difference in shape and size of spectrum. If there is any significant change represents interaction between drug and excipients.

9.5.PREPARATION OF STANDARD CURVE

Preparation of 0.1 M Hydrochloric acid:

Accurately measure 8.5 ml of hydrochloric acid and sufficient water to make upto 1000 ml.

Preparation of stock solution:

Accurately weigh 100 mg of Famotidine and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl.

Preparation of standard solution:

Pipette out 10 ml of the above solution and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl. Then from the standard stock solution withdraw 2ml, 4ml, 6ml, 8ml, and 10ml into five 100 ml different volumetric flasks. Then make up the volume to 100 ml with 0.1M Hcl to get 2, 4, 6, 8, 10 µg/ml concentration.

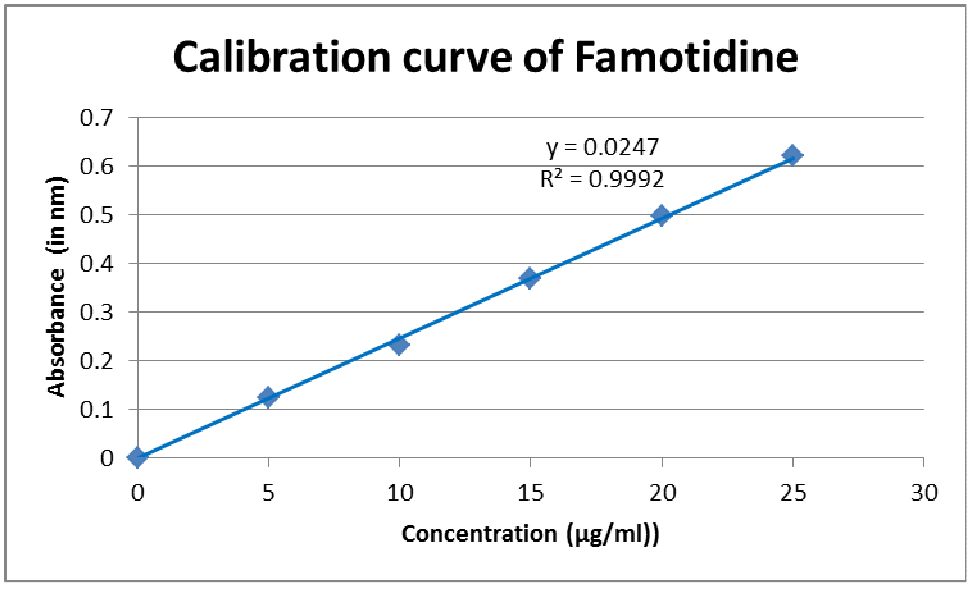
CALIBRATION CURVE OF FAMOTIDINE:

The absorbance of the prepared stock solutions was measured at 266 nm in an UV spectrophotometer. Plot a graph between concentration (in µg/ml) vs absorbance (in nm) on X-axis and Y-axis respectively.

Table no. 8. Calibration curve of Famotidine

S.no.	Concentration(in µg/ml)	Absorbance (in nm)
1.	0	0.000
2.	5	0.123
3.	10	0.233
4.	15	0.369
5.	20	0.497
6.	25	0.621
Slope	0.0247	
R^2	0.9992	

Fig.no.15 .Calibration curve of Famotidine



10. FORMULATION AND DEVELOPMENT OF FAMOTIDINE TABLETS

Table.no.9: Formulation of Famotidine tablets

INGREDIENTS(in mg)	FORMULATION BATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
HPMC K4M	0	30	0	0	30	30	0	30
HPMC K15M	0	0	30	0	30	0	30	30
HPMC K100M	0	0	0	30	0	30	30	30
$NaHCO_3$	20	20	20	20	20	20	20	20
Bees wax	30	30	30	30	30	30	30	30
Lactose	98	68	68	68	38	38	38	8
Magnesium sterate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Average weight	200	200	200	200	200	200	200	200

10.1 STEPS INVOLVED IN FORMULATION:

a) Sieving:

The ingredients were accurately weighed. Famotidine was sieved from mesh no. 80 then, HPMC K4, HPMC K15, HPMC K100, Sieved through mesh no. 80.

b) Melting:

White bees wax was melted in a chinadish.

c) Mixing:

Add Famotidine drug on molten mass and stirred well to mix. Then add HPMC polymer, sodium bicarbonate and lactose and mix it well.

d) Granulation:

Then the mass was allowed to cool to room temperature and then scrapped from chinadish. The coherent mass was passed through sieve no. 20.

e) Lubrication:

The resulting granules were mixed with magnesium stearate and talc.

f) Compression:

The lubricated granules were compressed into tablets using standard concave punch with 10 station rotary Proton mini press machine and keeping average weight of 200 mg.

After compression weight variation, Friability, dissolution and assay test were carried out.

11. EVALUATION

11.1. Pre-compression parameters:

1. Angle of repose:

Take a small quantity of powder(5 gm) in a cone shaped funnel and fix it to a holder at an appropriate height say 6 cm above the surface. Place a graph sheet below it. The sample was passed slowly through the funnel. The height of the powder heap was formed. Then measure the circumference of the heap by drawing with the pencil on the graph sheet. The radius of the heap was measured. The angle of repose is calculated by using the following formula. This is repeated five times for accurate results.

$$Ø = \text{Tan}^{-1} h/r$$

Where, h = height of file

R= radius of the base of the pile

Ø = angle of repose

The results were tabulated in table.

2.Bulk density and Tapped density:

Weigh a small quantity of the powder (w) was carefully poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus) set for 500 taps and after that, the volume (v_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk Density} = W/V_0$$

$$\text{Tapped Density} = W/V_f$$

Where, V_0= Initial volume,

V_f = final volume

The results were tabulated in table.

3. Compressibility index and Hausner ratio:

The compressibility index and hausner ratio are calculated by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:

$$\text{Compressibility index} = P_{tapped} - P_{bulk} / P_{tapped} \times 100$$

$$\text{Hausner ratio} = P_{tapped} / P_{bulk}$$

The results were tabulated in table.

11.2. EVALUATION OF FORMULATED TABLETS OF FAMOTIDINE[20]

All the formulated sustained release tablets were evaluated for following official and unofficial parameters.

1. Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in a none deviate by more than twice the percentage shown.

$$\% \text{ deviation} = \frac{\text{tablet weight-average weight}}{\text{Tablet weight}} \times 100$$

Observation:

The average weight and standard deviation of the tablets of each batch were given.

Weight variations Specification

Table No: 10. Weight variations Specification as per IP

Average weight of tablets(mg)	Maximum % difference allowed
Less than 80	10
80- 250	7.5
Above 250	5

2. Dimensions

Control of physical dimension of the tablets thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using digital Vernier calipers. The thickness of tablets is mostly related to the tablet hardness can be used as initial control parameter.

Six tablets were randomly selected from each batch and their thickness was measured by using Digital Vernier caliper.

3. Hardness[20]

It is determined to get perfect compactness during shipping, coating, and packaging and to get proper shape and design. Hardness was measured by using hardness tester. (Pfizer hardness tester) for each batch six tablets were tested. The force required to break the tablet is recorded by the unit is Kg/cm^2.

Observation:

The measured hardness of tablets of each batch was range from 6-16Kg/cm^2.

4. Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for every 4 minutes. After revolution the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\%F = \{1-(W_t/W)\} \times 100$$

Where, %F=friability in percentage

W=initial weight of tablets after revolution

Observation:

All the formulated batches were found under acceptable limit of 0.1- 0.6 as specified in IP.

5. Buoyancy Lag Time[22]

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

The results were tabulated in table.

6. Floating Time[23]

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

7. **Dissolution study:**

Preparation of buffer:

Measure 8.5 ml of HCL in a 1000 ml volumetric flask and make up the volume to 1000 ml using distilled water.

Requirements:

Medium: 0.1N Hcl

Volume: 900 ml

Apparatus: USP II (paddle)

RPM: 100

Time: upto 12 hrs

Temperature: 37^0 c $\pm$ 0.5^0c

λmax : 266 nm

Perform the test on six tablets one tablet in each dissolution vessel containing 900 ml of 0.1 N Hcl maintained at 37^0c $\pm$ 0.5^0c. at specific time withdrawn required amount of sample and replace same amount of 0.1N HCL (maintain sink condition), then absorbance was taken and calculate percentage release.

$$\% \text{ purity} = \frac{\text{absorbance} * 900 * \text{dilution}}{\text{Slope} * 1000 * \text{label claim}} * 100$$

8. Assay:

Crush 20 tablets and weigh equivalent to 20 mg famotidine and dissolved in 0.1N Hcl and make up the volume to 100 ml. From that, withdraw 10 ml and diluted to 100 ml with 0.1 N Hcl. Read the absorbance at 266 nm in UV spectrophotometer.

9. **Kinetics of drug release**

The invitro dissolution profile of all batches were fitted to Zero order, first order, Higuchi model and Koresmeyer-Peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.

- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

Zero-order kinetics

Zero order release would be predicted by the following equation:

$$\mathbf{A_t = A_o - K_o t}$$

A_t - Drug release at time't'

A_o - Initial drug concentration

K_o - Zero-order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vs time and the plot is linear, then the data obeys zero-order equal to K_o.

First order kinetics:

First order release would be predicted by the following equation:

$$\mathbf{Log\ C = log\ C_o - K_t / 2.303}$$

C - Amount of drug remained at time't'

C_o - Initial drug concentration

K - First-order rate constant (hr^{-1})

When data is plotted as log cumulative % remaining Vs time yields a straight line, and then the release obeys first order kinetics. The constant 'K' obtained by multiplying 2.303 with the slope values.

Higuchi's Model:

Drug release from the matrix devices by diffusion has been described by Following Higuchi's classical diffusion equation:

$$\mathbf{Q = [D\varepsilon/\tau\ (2A - \varepsilon CS)\ CSt]^{1/2}}$$

Q - Amount of drugreleased at time't'

D - Diffusion coefficient of the drug in the matrix

A - Total amount of drug in unit volume of matrix

CS - The solubility of drug in the matrix

ε - Porosity of the matrix

τ - Tortuosity

t - Time at which amount of drug released

When the data is plotted as Cumulative % drug released Vs square root of time yields a straight line, indicating that drug release follows diffusion mechanisms. The slope is equal to 'K'.

Korsmeyer – Peppas model:

To study the mechanism of drug release from the microspheres, the invitro release data were fitted to the well-known exponential equation (Korsmeyer – Peppas model), which is often used to describe the drug release behaviour from polymeric systems.

$$Mt/M\alpha = Kt^n$$

Mt/Mα - The fraction of drug released at time't'

K-Constant incorporating structural and geometrical characteristics of the drug/polymer system

N-Diffusion exponent related to the mechanism of drug release

When the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept.

Mechanism of drug release as per Korsmeyer - Peppas equation / Peppas model.

Table. No. 12: Mechanism of drug release

S.No	n value	Drug release
1	0 –0.5	Fickian release
2	0.5 – 1.0	Non-Fickian release
3	>1.0	Class II transport

12. RESULT AND DISCUSSION

12.1. Preformulation studies:

12.1.1. Organoleptic properties:

The tests were performed as per the procedure. The results were tabulated below.

Table.no.13. organoleptic properties

Test	Specifications/limits	Observations
Colour	White to pale yellow	White powder
odour	Odourless	Odourless

The result complies as per specifications.

12.1.2. Physical properties:

Angle of repose:

It was determined as per procedure. The results were tabulated below.

Table.no.14. flow properties

Material	Angle of repose
Famotidine	27.14^0

The results show that the drug having poor flow.

Bulk density and tapped density:

It was determined as per procedure. The results were tabulated below.

Table no. 15.bulk density and tapped density

Material	Bulk density(gm/ml)	Tapped density(gm/ml)
Famotidine	0.48	0.44

Powder compressibility:

It was determined as per procedure. The results were tabulated below.

Table no. 16.powder compressibility

Material	Compressibility index	Hausner's ratio
Famotidine	11.27	1.44

Melting point:

It was determined as per procedure. The results were tabulated below.

Table no.17. Melting point

Material	Melting point range	Result
Famotidine	163.5 ° C	163 ^{0}c

The result indicates that the Famotidine drug was pure one.

12.1.3. SOLUTION PROPERTIES

P^H of the solution:

It was determined as per procedure. The results were tabulated below.

Table no. 18. P^H of the solution

Material	test	Specification	observation
Famotidine	P^H	5-6(1% aqueous solution)	6.22

The result indicates that the Famotidine drug was pure one.

Solubility:

It was determined as per procedure. The results were tabulated below.

Table no.19 . Solubility

Material	test	Specification	observation
Famotidine	Solubility	Freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.	Complies

The result complies as per specification.

12.1.4. Drug-excipient compatibility studies:

Discussion:

The FT-IR peaks were observed that there is no change in the spectrum representing that there is no interaction between the drug and polymers and other excipients. These peaks play a vital role with respect to drug release.

Table no. 20. Drug-excipient compatibility

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + HPMC K4 M	White powder	No change	No change	Yes
Drug + HPMC K15 M	White powder	No change	No change	Yes
Drug + HPMC K100 M	White powder	No change	No change	Yes

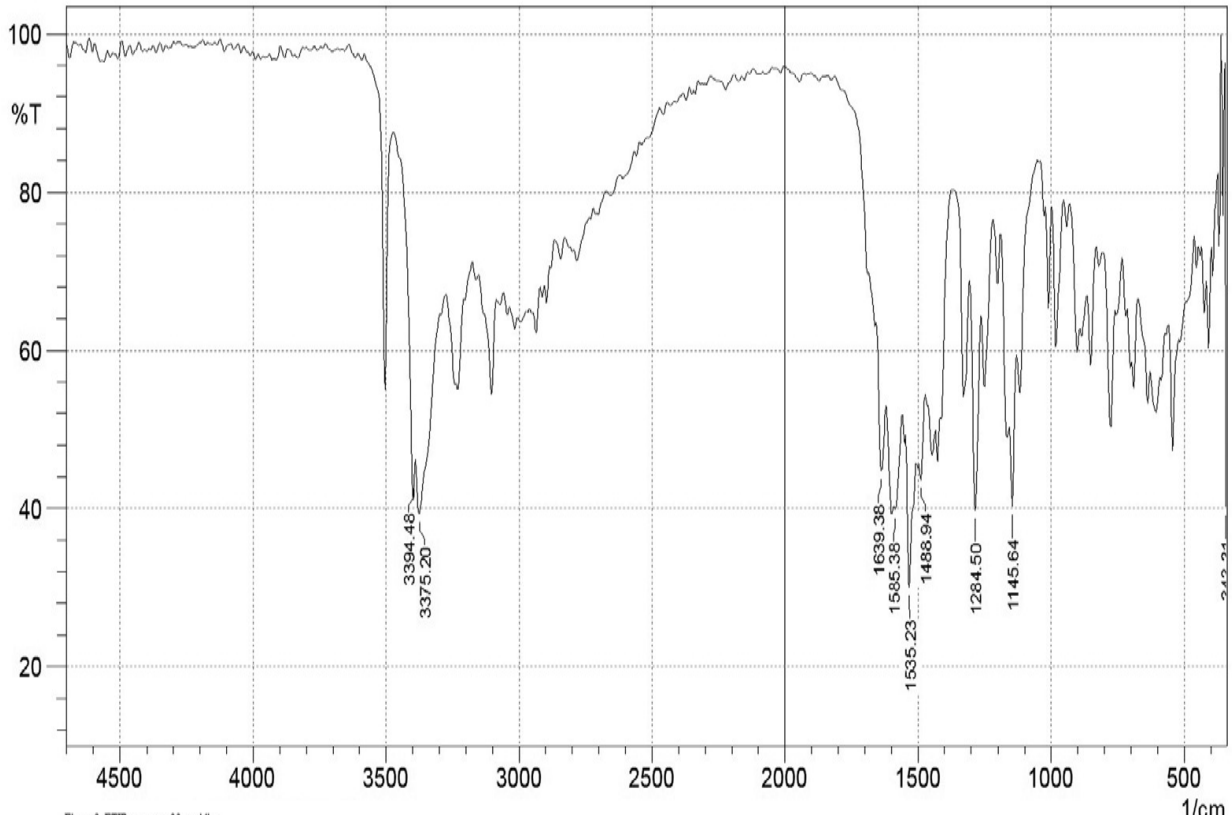


Fig. no. 16. FTIR of Famotidine

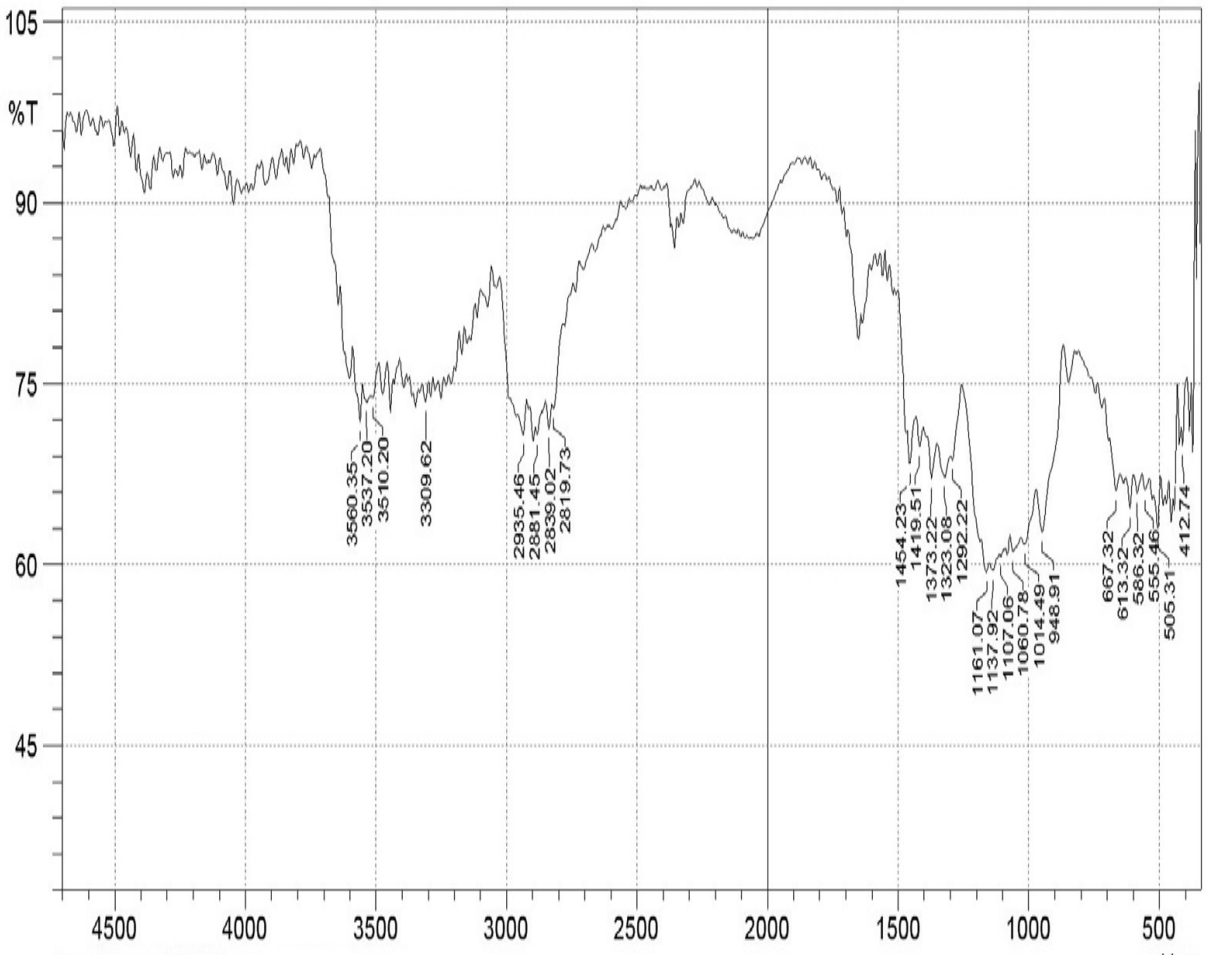


Fig. no. 17. FTIR of HPMC

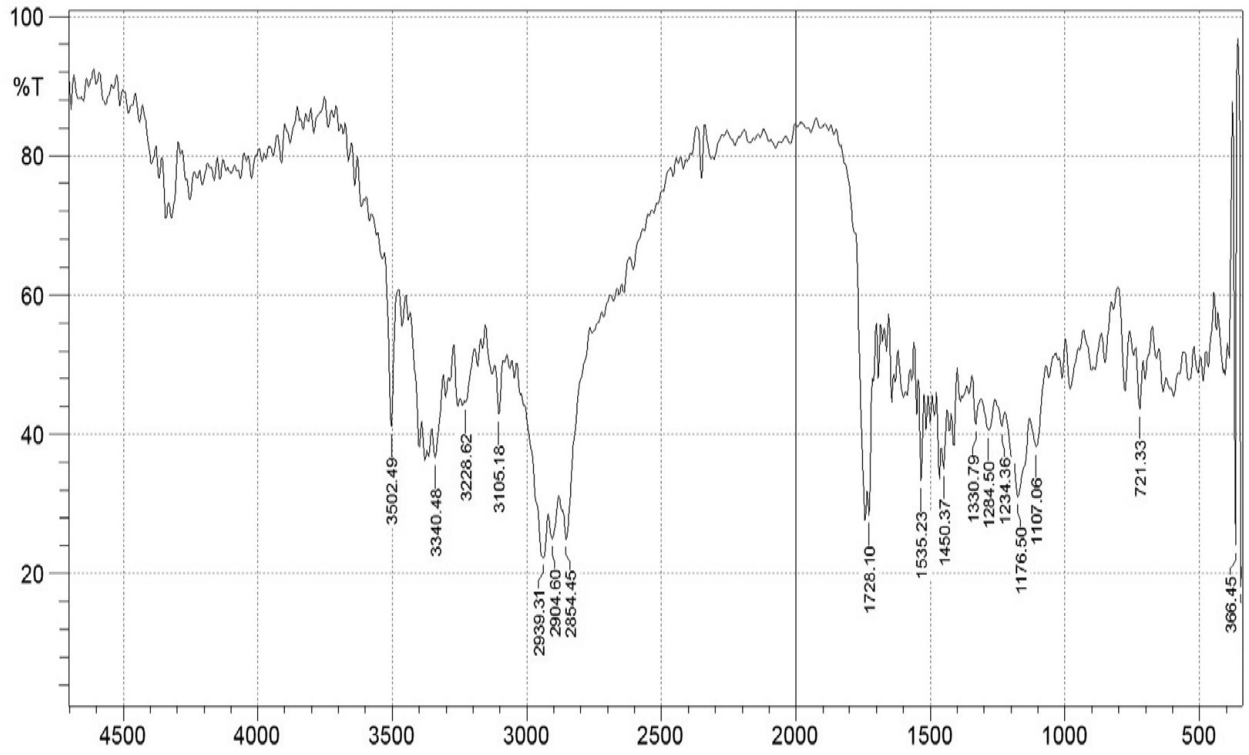


Fig. no. 18. FTIR of Famotidine + excipients

12.1.5. Evaluation of granules:

Table.no.21. showing results of angle of repose, bulk and tapped density, Carr's index, hausner ratio

Batch no.	Angle of repose(^{0})	Bulkdensity (gm/ml)	Tappeddensity (gm/ ml)	Carr's index(%)	Hausner ratio
F1	26 ^{o} 32'	0.2891	0.3503	14.04	1.21
F2	24^o 64'	0.2845	0.3394	15.68	1.22
F3	28^o 59'	0.2924	0.3349	11.94	1.13
F4	26^{o}12'	0.2875	0.3446	13.96	1.16
F5	23^o 62'	0.2862	0.3420	15.13	1.19
F6	24^{o}74'	0.2677	0.3214	13.92	1.15
F7	24 ^{o} 77'	0.2743	0.3242	15.42	1.19
F8	26 ^{o} 56'	0.2847	0.3177	10.38	1.11

Discussion:

The angle of repose for the formulations F1-F8 was found to be in the range 23^0.62' to 28^0.59' shows good flow.

Compressibility index for the formulations F1-F8 found between 10.38% to 15.6% indicating that the blend has good flow property for compression.

12.1.6. EVALUATION OF FAMOTIDINE TABLETS

Table no. 22.weight variation and friability

Batch no.	Weight variation	Friability	Content uniformity
F1	± 1.52	0.23	99.65
F2	±2.37	0.34	99.74
F3	± 1.87	0.21	98.34
F4	± 1.41	0.27	99.44
F5	±1.86	0.18	100.38
F6	±2.56	0.28	99.96
F7	±2.35	0.29	99.47
F8	±1.93	0.19	99.35

Discussion:

The weight variation of the above tablets are in the range of ± 1.23 to 3.09 %(below 5%) complying with the pharmacopoeial standards.

The friability of the tablets are in the range of 0.18 % to 0.34% (below 1%) complying with the pharmacopoeial standards.

The content uniformity of the tablets are in the range of 99.37 to 100.38% complying with the pharmacopoeial standards.

12.1.7. THICKNESS AND HARDNESS:

Table no. 23.Thickness and hardness

Batch no.	Thickness(mm)	Hardness(kg/cm^2)
F1	5.2±0.01	6.2
F2	5.1±0.02	7.1
F3	5.3±0.01	6.5
F4	5.1±0.03	6.9
F5	5.2±0.01	6.3
F6	5.3±0.04	7.2
F7	5.5±0.01	7.5
F8	5.3±0.01	6.4

Discussion:

The thickness of the formulations was found to be in the range of 5.1±0.01 to 5.5±0.01 mm.

The hardness of the tablets was found to be in the range of 6.2 to 7.5 kg/cm^2 indiacting a satisfactory mechanical strength.

12.1.8. BUOYANCY LAG TIME AND TOTAL FLOATING TIME

Table no. 24. Showing buoyancy lag time and total floating time

Batch no.	Buoyancy lag time	Total buoyancy time(hrs)
F1	624	15
F2	96	3
F3	90	6
F4	84	12
F5	171	5
F6	63	10
F7	44	15
F8	39	14

Discussion:

From the results formulations F1, F4, F7, F8 shows good buoyancy,all formulations showed buoyancy upto 12 hrs.

12.2.In-vitro release profile:

Table.no.25. *in-vitro* release profile

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	8.65	24.79	15.13	7.24	21.32	13.76	5.91	12.25
2	13.12	58.12	34.67	12.09	43.13	24.27	11.64	16.79
3	17.75	95.39	46.21	17.62	67.08	30.14	17.08	22.47
4	25.34		63.90	23.98	96.34	39.51	25.42	26.75
5	29.59		76.39	31.56		46.24	29.32	30.54
6	34.23		96.14	39.34		53.69	31.13	37.67
7	41.09			47.87		67.76	36.41	43.34
8	47.23			55.23		80.09	40.69	49.50
9	53.98			64.42		89.13	46.86	54.71
10	58.14			73.7		97.43	53.63	60.92
11	61.17			84.54			57.20	68.43
12	67.91			96.78			62.32	72.19

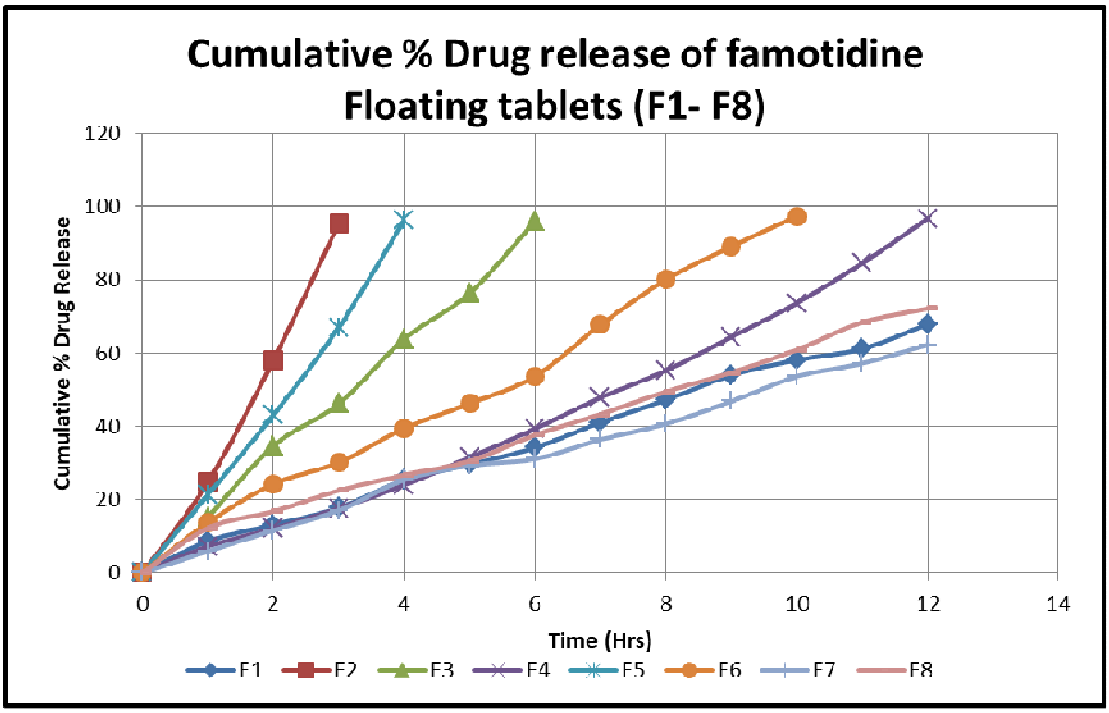


Fig. no. 19. Showing in-vitro drug release profile for F1-F8 formulations

From the in-vitro dissolution study of all formulations, formulation F1 gave 84% release at the end of 24th hour, hence F1 have choosen as best formulation.

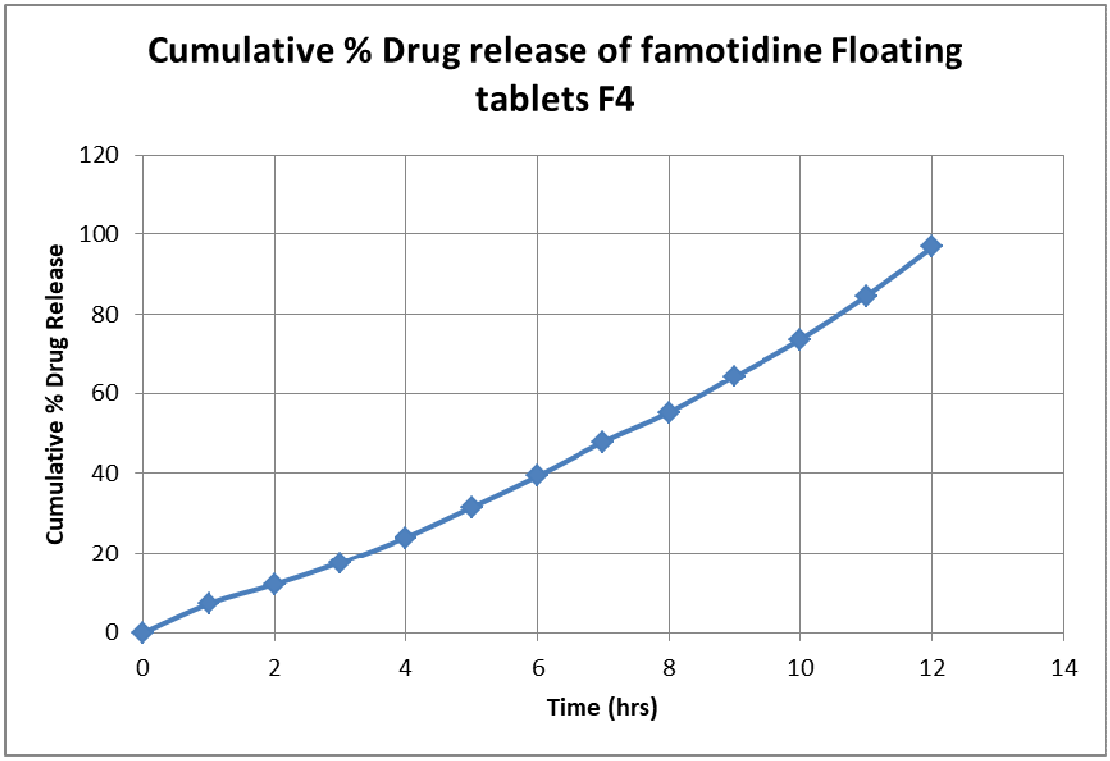


Fig. no. 20. Showing in-vitro release profile of best formulation(F10)

12.3. DRUG RELEASE KINETICS:

Fig. No.26: Drug release kinetics:

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released
0	0	100	0.000	2.000	0.000	0.000	100
1	7.24	92.76	1.000	1.967	0.000	0.860	7.24
2	12.09	87.91	1.414	1.944	0.301	1.082	4.85
3	17.62	82.38	1.732	1.916	0.477	1.246	5.53
4	23.98	76.02	2.000	1.881	0.602	1.380	6.36
5	31.56	68.44	2.236	1.835	0.699	1.499	7.58
6	39.34	60.66	2.449	1.783	0.778	1.595	7.78
7	47.87	52.13	2.646	1.717	0.845	1.680	8.53
8	55.23	44.77	2.828	1.651	0.903	1.742	7.36
9	64.42	35.58	3.000	1.551	0.954	1.809	9.19
10	73.7	26.3	3.162	1.420	1.000	1.867	9.28
11	84.54	15.46	3.317	1.189	1.041	1.927	10.84
12	96.78	3.22	3.464	0.508	1.079	1.986	12.24

Fig. no. 21: Zero Order Kinetic Model

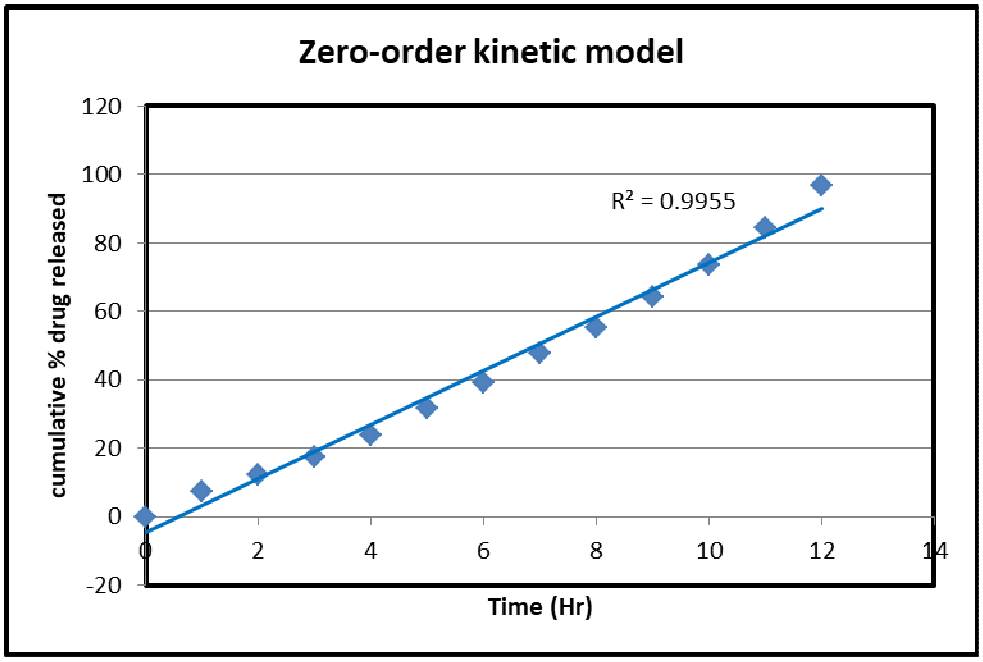


Fig. no. 22: First Order Release Kinetics

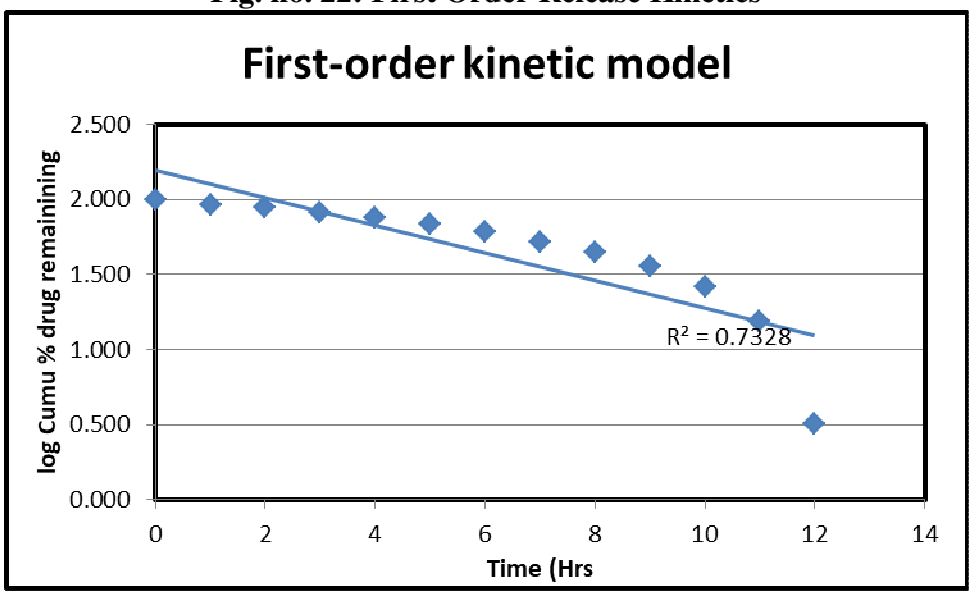


Fig. no. 23: Higuchi model

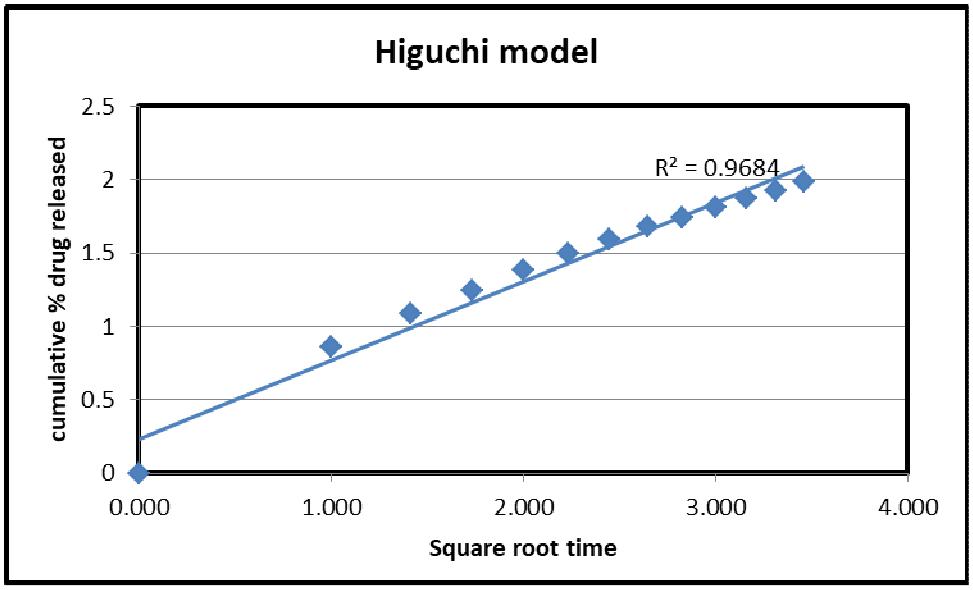


Fig. no. 24: Korsemeyer Peppas Model

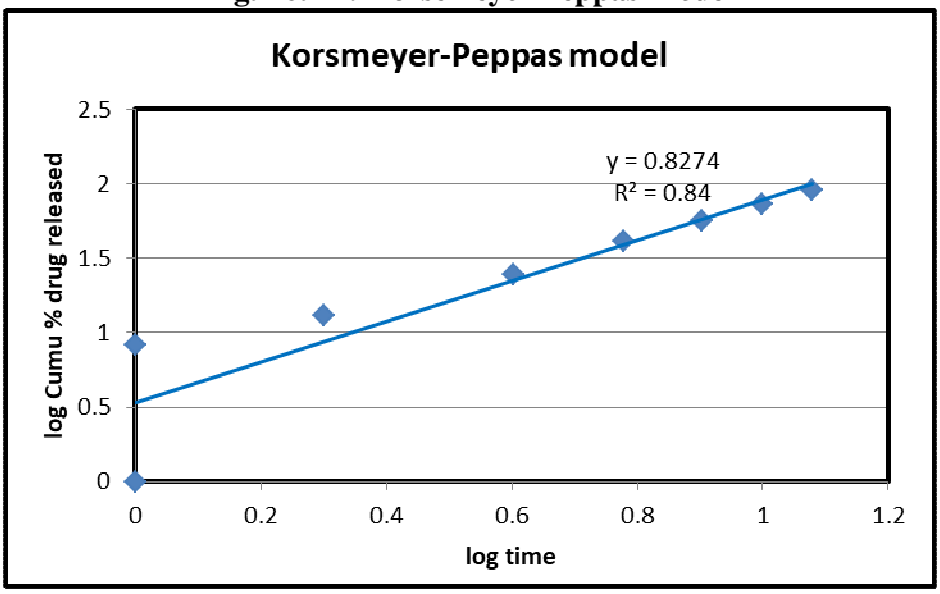


Table.No:27. Regression coefficient of F10

Formulation	Regression coefficient (R^2) value			
	Zero-order	First order	Higuchi	Korsmeyer – Peppas (n value)
Famotidine tables	0.9955	0.7328	0.9684	0.84 (0.8274)

N value = 0.8274

The regression coefficient values and n values show that the drug releases follow Non - Fickian release.

At initial

After 45 sec

After 4 hour

Fig. No: 25. Buoyancy of formulation F4.

13. SUMMARY

The present study involves the formulation and evaluation of gastroretentive drug delivery of Famotidine tablets. This type of drug delivery helps to retain the drug in the stomach. The swelling property of the formulation helps to retain the drug in the stomach, by swelling to such an extent so that cannot pass out of the stomach.

Preformulation studies which include Organoleptic properties, Bulk and Tapped densities, Carr's index, Hausner's ratio, Melting point, P^H , Solubility, were carried out are as per IP specifications.

Drug-excipient compatibility studies were performed which shows that there is no interaction between drug and polymers.

Evaluation studies have been performed for tablets include friability, hardness, weight variation, content uniformity, buoyancy studies are as per IP specifications.

Drug release studies have been performed by using 0.1N Hcl for 12 hrs. These studies have shown that the formulation F4 gave better drug release upto 12 hrs. which is formulated with HPMC K100 M.

14. CONCLUSION

Floating tablets with sustained release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

Moreover, floating mechanism doesn't require any complex technology and hence, easy to adopt. Hence, it can be employed in various developmental studies based on requirement.

Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development to treating various diseases.

Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

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